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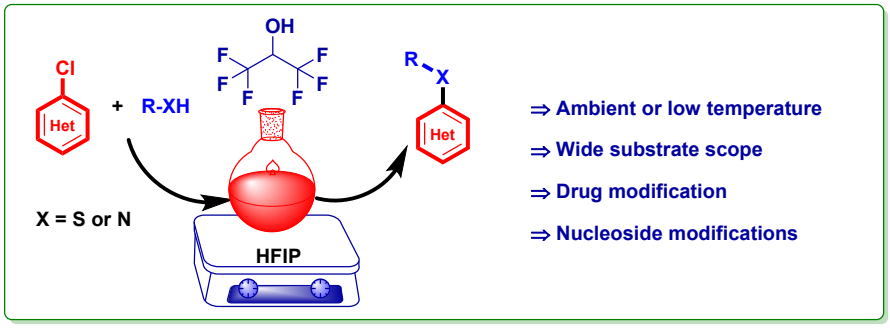
Yuvraj B. Bhujabal,[a] Kamlesh S. Vadagaonkar,[a] Aniket Gholap,[a] Yogesh S. Sanghvi,[b] Rambabu Dandela,[c] and Anant R. Kapdi[a,c]*

[a]Department of Chemistry, Institute of Chemical Technology, Nathalal Parekh road, Matunga, Mumbai-400019, India.

[b]Rasayan Inc., 2802, Crystal ridge road, Encintas, California, 92024-6615, USA.

[c]Department of Chemistry, Institute of Chemical Technology-Indian Oil Odisha Campus, IIT Kharagpur extension centre, MouzaSamantpuri, Bhubaneswar-751013, Odisha, India.

E-mail: ar.kapdi@ictmumbai.edu.in



ABSTRACT

A highly efficient and an unprecedented HFIP promoted low temperature aromatic nucleophilic substitutions of chloroheteroarenes has been performed using thiols and (secondary) amines under base-free and metal-free conditions. The developed protocol also provides excellent regio-

control for the selective functionalisation of dichloroheteroarenes, while the utility of the protocol was demonstrated by the modification of a commercially available drug Ceritinib.

INTRODUCTION

Heteroarenes are important structural motifs commonly found in a variety of drugs,[1] agrochemicals[2] and functional materials[3] of commercial relevance. Presence of certain functionalities on the heteroarene backbone has been found to greatly enhance the bioactivity of the derived molecules. Thioethers[4] and amine functionalities when incorporated onto the heteroarene has found applications as fungicide (TCMTB),[5] immunosuppressive agent (Imuran, Azathioprine),[6] anti-breast cancer agent (Buparilsib),[7] anti-neoplastic agent (ZSTK474),[8] anti-hypertension agent (Uptravi)[9] and many others (Figure 1).

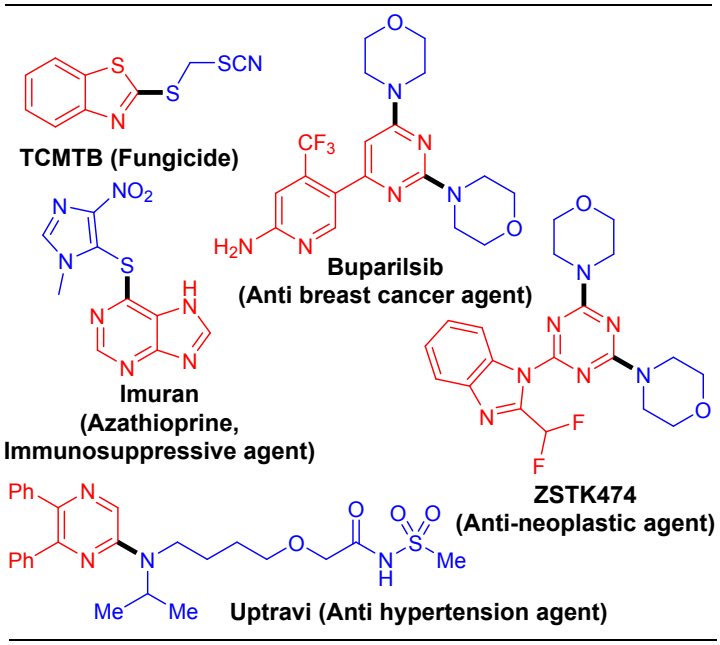


Figure 1. Thioether and amine functionality containing commercial heteroarene-based drugs and agrochemicals.

Access to these molecules in the past has been through a variety of general synthetic procedures (less efficient, time-consuming and suffering from tedious work-up procedures),[10] metal-mediated processes[11,12] (low reactivity and expensive) as well as metal-free (or/and base-free)S_NAr-type reactions[13] (commonly carried out at very high temperatures and poor reactivity). The problems listed with the above synthetic procedures make it highly desirable to develop simple, efficient and scalable protocol for addressing these issues. A possible solution to this problem could be achieved by taking into consideration the rate-enhancing effects of certain solvents that have been reported in literature.[14]

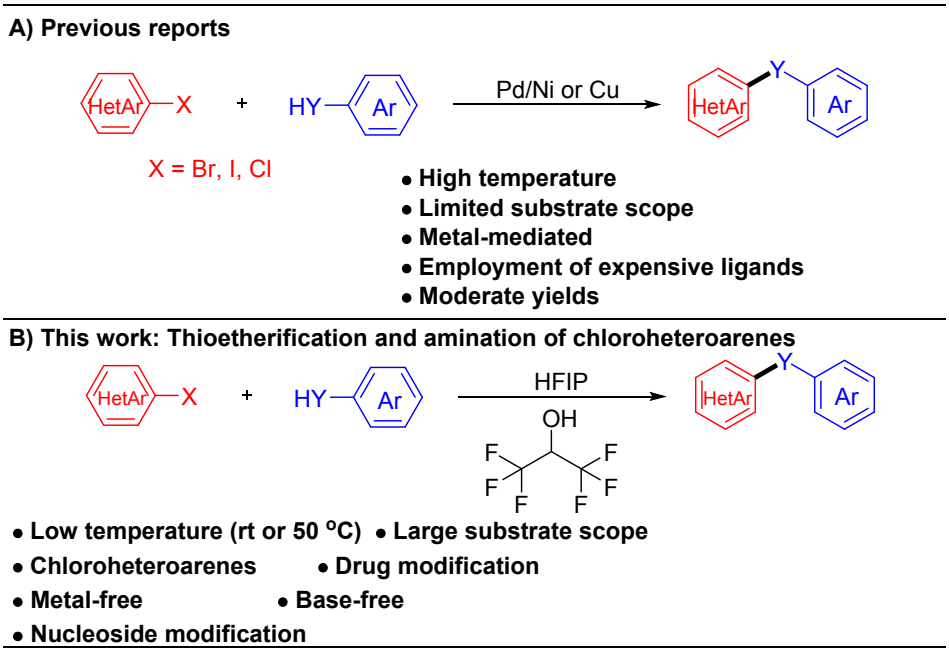


Figure 2. Prior art and current work for thioetherification and amination.

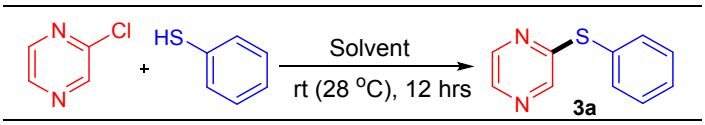
Hexafluoro-2-propanol[15] (HFIP) is a highly versatile compound that has found applicability as additive, co-solvent and most importantly a promoting solvent in a variety of synthetic transformations under metal-mediated[16] or metal-free conditions.[17] Its role as a promoter could be envisaged due to the several unique properties, such as strong hydrogen bond donor,fairly

acidic nature and the ability to ionise substrates. A combination of these properties has contributed immensely to its employment as a promoting solvent in processes such as Friedel Crafts reactions,[18] Diels Alder reactions,[19] C—H bond functionalizations,[20]Aza-Michael reactions,[21]Passerini reaction,[22] Halogenation reactions[23] and many others involving aliphatic as well as aromatic substrates. In spite of the tremendous success obtained with HFIP in different reactions, its applicability to promote aromatic nucleophilic substitutions on aromatic or heteroaromatic substrates remains to date unexplored. The current report discusses in detail the unprecedented promoting effect of HFIP as a sole solvent for ambient temperature thioetherification and low temperature amination of chloroheteroarenes under metal-free and base-free conditions (Figure 2).

RESULTSAND DISCUSSION

At the outset of the studies, optimisation of conditions for the thioetherification of chloroheteroarenes was performed with different solvents. Thioetherification via metal-mediated processes suffers from a major drawback of catalyst poisoning that has limited their synthesis at ambient temperature.

Table 1.OptimisationTable for Room Temperature Thioetherification[a]



entry	solvent	catalyst	base (equiv.)	solvent (mL)	time (h)	yield (%)
1	DMF	--	--	2	12	Trace

2	IPA	--	--	2	12	Trace
3	Toluene	--	--	2	12	NR
4	Ethanol	--	--	2	12	Trace
5[b]	DMF	HFIP	--	2	12	Trace
6	TFA	--	--	2	12	79
7	TFE	--	--	2	12	65
8	HFIP	--	--	2	12	87
9	**HFIP**	**--**	**--**	**1**	**12**	**94**
10	HFIP	--	--	3	12	86
11[c]	HFIP	--	Na_2CO_3(2.0)	2	12	Trace

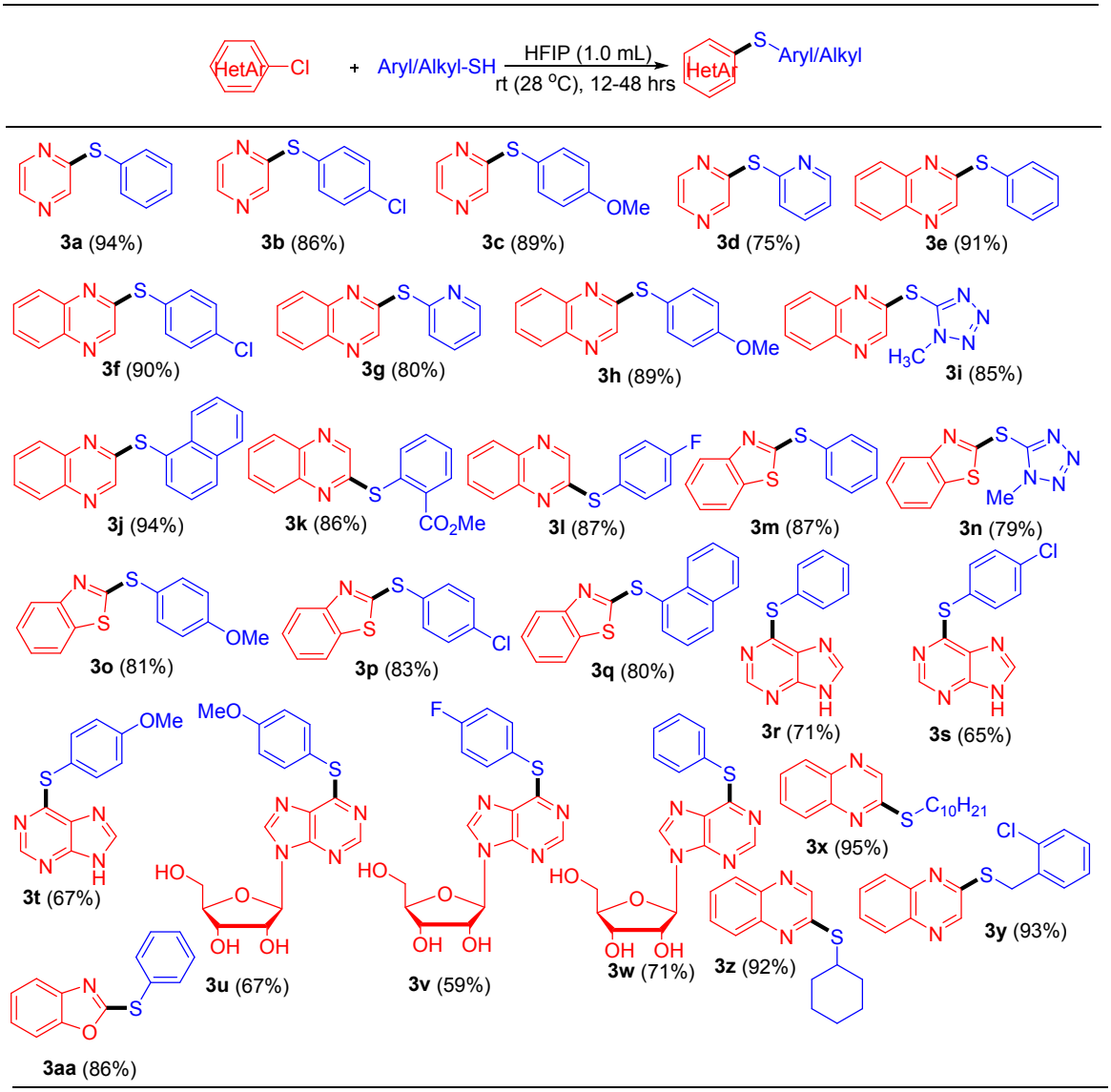
[a]Reaction conditions: 2-chloropyrazine (1.0 mmol), thiophenol (1.2 mmol) and solvent (1-3 mL) were stirred at rt (28 ^oC)for 12 h in a pressure vial. [b]Reactionin the presence of catalytic amount of HFIP. [c]Reactionin the presence of Na_2CO_3 (2.0 equiv.) as a base.

To address this problem, it was decided to explore the possibility of performing the metal-free thioetherification at ambient temperature between 2-chloropyrazine and thiophenol (Table 1). Polar solvents such as dimethylformamide and isopropanol (Table 1, entries 1 and 2) failed to provide any product as was the case with toluene and ethanol (Table 1, entries 3and 4). The employment of HFIP as an additive to DMF also failed to provide any product (Table 1, entry 5). Fluorinated alcohols in the past have shown promising results in promoting substitution reactions in different substrates. With this in mind, trifluoroacetic acid (TFA), trifluoroethanol (TFE) and HFIP were employed as the solvents without the addition of any base. Interestingly, fluorinated solvents provided good to excellent yield of the desired thioetherified product with best results obtained with HFIP (Table 1, entries 6-8 respectively). Quantity of HFIP used for the reaction also

had a pronounced effect on the nucleophilic substitution reaction as 1.0 mL of HFIP was found to be the optimum concentration for obtaining maximum yield (Table 1, entry 9), while addition of base failed to provide any product with deprotonation of HFIP as the possible reason for the loss in activity (Table 1, entry 11).

With a simple, metal-free and base-free protocol in hand, we explored the substrate scope for thioetherification with a wide variety of chloroheteroarenes and aryl as well as alkyl thiols.With good to excellent yields obtained for simple heteroarenes at ambient temperature (**3a-q**, Scheme 1) the thioetherification protocol was also extended to 6-chloropurine with similar results (**3r-t**, Scheme 1). Modification of 6-chloro purine riboside is a synthetically challenging prospect given the lability of the glycosidic bond due to its temperature sensitivity. Thioetherification of 6-chloro purine riboside at ambient temperature would therefore be ideal and unprecedented.[24]This was achieved in good yields using the developed protocol promoted by HFIP (**3u-w**, Scheme 1). Besides arylthiols, the developed protocol also was tested for the employment of alkylthiols as nucleophilic partners with very good yields obtained for their coupling with 2-chloroquinoxaline (**3x-z,** Scheme 1). Oxygen containing heterocycles such as 2-chlorobenzoxazole was also thioetherified efficiently under the developed reactions conditions (**3aa**, Scheme 1).Successful development of room temperature thioetherification protocol allowed us to explore the possibility of carrying out amination of chloroheteroarenes.

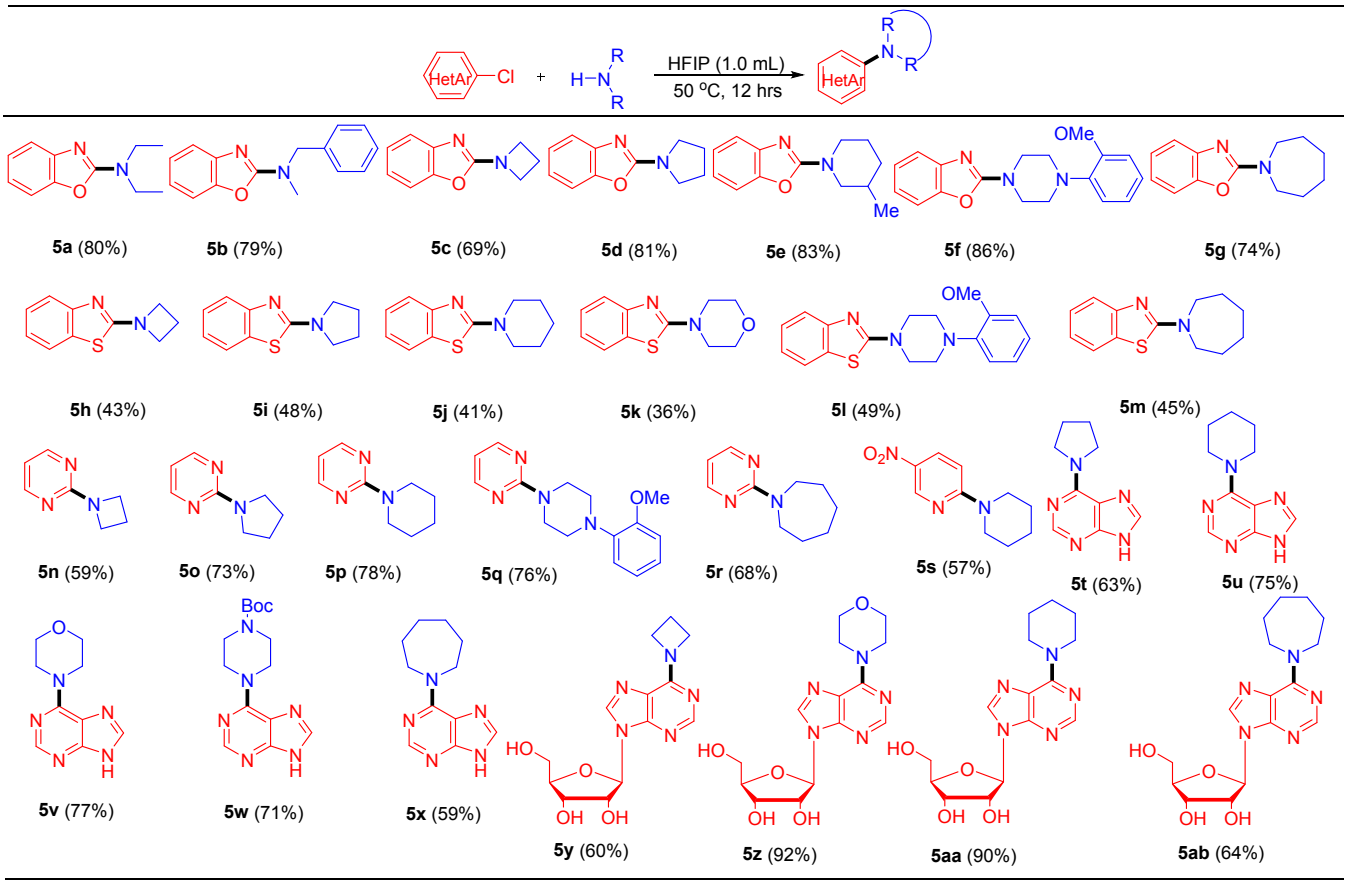
Scheme 1.Scope Studies for Thioetherificationof Chloroheteroarenes at Low Temperature in HFIP



Amination of chloroheteroarenes was next to be undertaken and at the outset it was observed that as compared to thioetherification, which proceeds at ambient temperature, amination requires slightly higher temperature (50 °C). Firstly, 2-chlorobenzoxazole was subjected to amination conditions with wide variety of secondary amines as it was observed initially that the primary amines provided poor reactivity. Secondary amines ranging from diethylamine, methyl benzylamine, azetidine, pyrrolidine, 3-methyl piperidine, 4-(2-methoxyphenyl)piperazine and azepanewere coupled efficiently with 2-chlorobenzoxazole (**5a-g**, Scheme 2). Next, 2-

chlorobenzothiazole was employed as the substrate, however in comparison to benzoxazole it was found to be less reactive providing lower yields of the aminated product (**5h-m**, Scheme 2).

Scheme 2.Scope Studies for Amination of Chloroheteroarenes at Low Temperature in HFIP

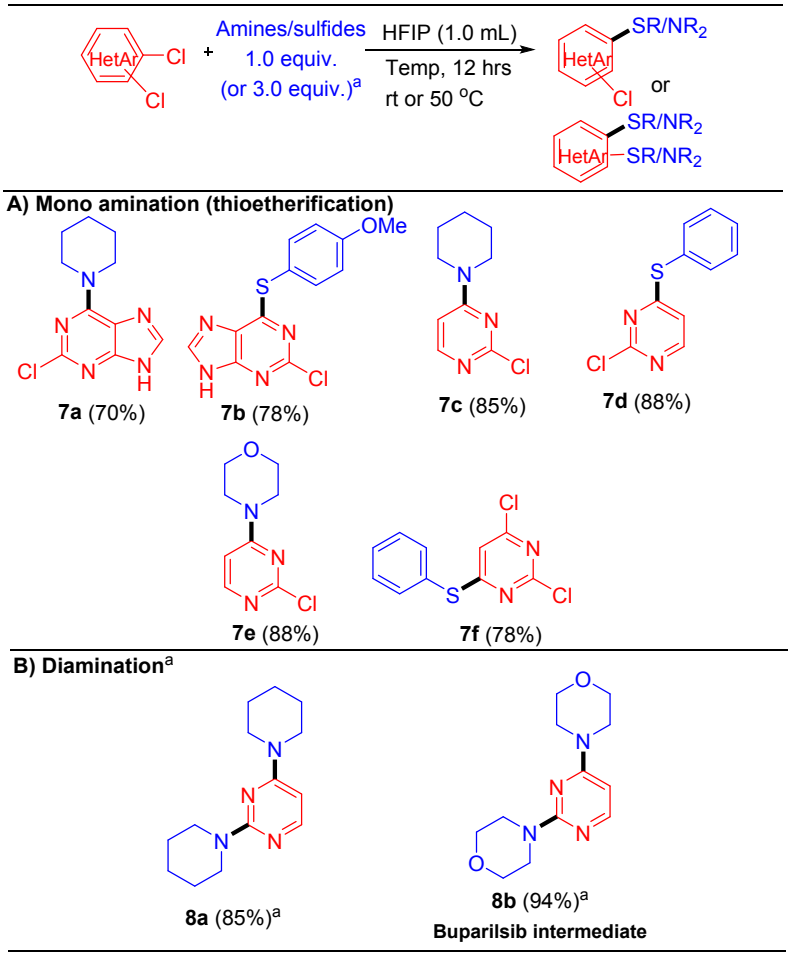


Improved yields were obtained with pyrimidine as 5 different secondary amines were coupled efficiently under the developed reaction conditions (**5n-r**, Scheme 2). Although, 2-chloropyridine was also subjected to amination, negligible product formation due to the possible protonation of pyridine N atom was observed. To address this issue, we envisaged the introduction of an electron-withdrawing group that would help promote the amination to proceed in the forward direction. Accordingly, 2-chloro-5-nitropyridine when reacted with secondary amines in HFIP at 50 °C yielded decent amount of the desired product (**5s**, Scheme 2). Purine

was next to be submitted to the amination conditions with different secondary amines providing good yields of the product (**5t-x**, Scheme 2), an observation which was also achieved in the case of 6-chloroadenosine providing molecules of synthetic relevance (**5y-z**, **5aa-ab**, Scheme 2).

Regioselectivity in synthesis is an important synthetic challenge that in the past has been explored extensively using metal-mediated processes.[25] Solvent-assisted regioselective reactions are rare and development of selective processes without the incorporation of metal is highly desirable. In literature, polyhalogenated heteroarenes have been effectively functionalized in a selective manner.[26]We envisaged HFIP to promote the selective mono-amination or thioetherification of dichloro or trichloroheteroarenes. 2,6-Dichloropurine, 2,4-dichloropyrimidine and 2,4,6-trichloropyrimidine were selected as substrates and amination as well as thioetherification was performed to provide mono-functionalised heteroarenes in good yields by the employment of a stoichiometric amount of nucleophiles (**7a-f**, Scheme 3A).

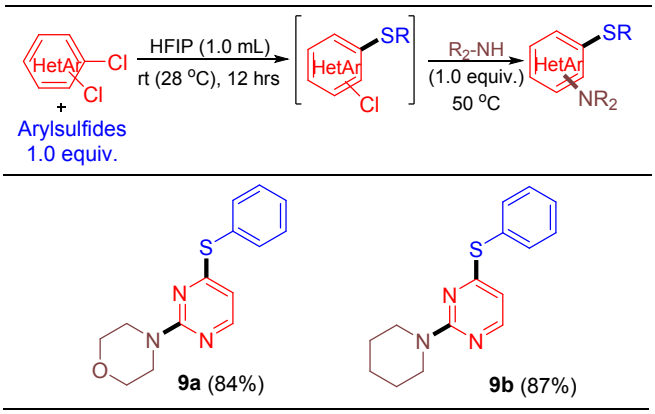
Scheme 3. Regioselective Modification of Polyhalogenated Heteroarenes



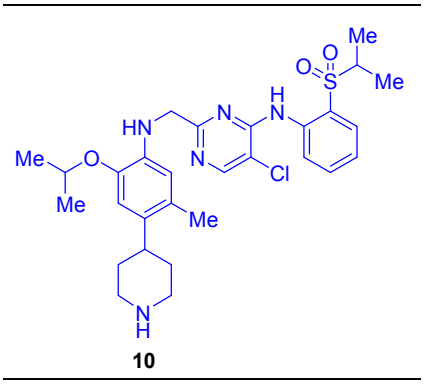
However, the employment of excess amount of amine (piperidine or morpholine) with dichloro heteroarenes provided diaminated products of which one was an important Buparilsib intermediate[7] (Buparlisib is a pan-class 1 phosphoinositide 3-kinase inhibitor) **8b** (**8a-b**, Scheme 3B). The above result suggests that the employment of HFIP as a promoter solvent has beneficial effect for obtaining selectivity in the given transformations. This was further exploited for the synthesis of unsymmetrically substituted heteroarenes via simultaneous thioetherification/amination protocol performed at different temperatures (**9a-b**, Scheme 4). The strategy employed involves an initial regioselective thioetherification carried out at ambient temperature followed by amination performed at an elevated temperature of 50 °C. Such a

synthetic strategy presents researchers with an easy and efficient method for accessing such diverse structural motifs.

Scheme 4. Unsymmetrically Substituted Heteroarenes via Simultaneous Thioetherification/AminationProtocol

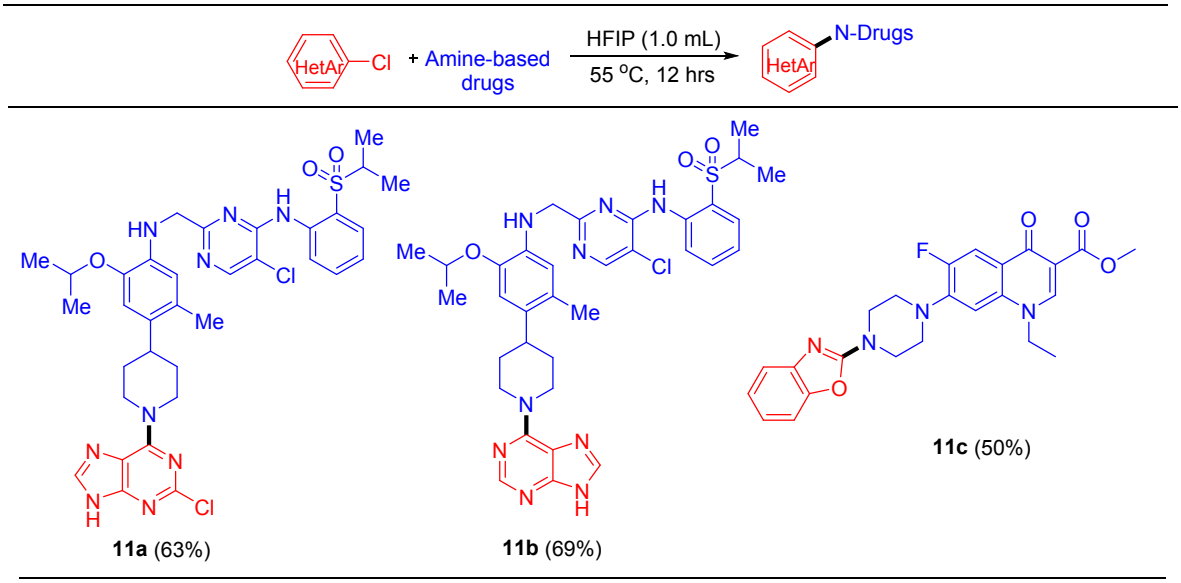


Synthetic utility of the developed protocol was demonstrated with the modification of a commercial anti-cancer drug, Ceritinib (**10**).[27]



The secondary amine (piperidine) structural feature under the HFIP promoted amination conditions coupled with 6-chloropurine and 2,6-dichloropurine in good yields (**11a-b**, Scheme 5).

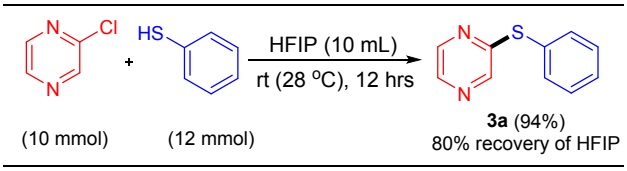
Scheme 5. Commercial Secondary Amine-Based Drug Modification



Similarly, another commercial drug, Norfloxacin could easily be modified using the developed protocol with chlorobenzoxazole interacting with the secondary amine of the drug (**11c**, Scheme 5).

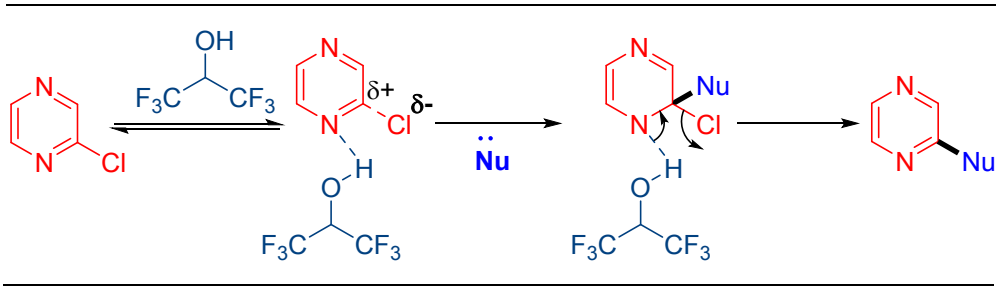
The development of a synthetically useful thioetherification and amination protocol for chloroheteroarenes allowed for the possibility to perform scale-up studies. With a 10 mmol reaction of 2-chloropyrazine carried out with 12 mmol thiophenol in 10 mL of HFIP at ambient temperature provided 94% of the desired product (Scheme 6). On completion of the reaction, HFIP was recovered up to 80% providing an opportunity to reuse the solvent for further application.

Scheme 6. Scale-up studies



Based on the results obtained with HFIP as a solvent and promoter a plausible mechanism has been put forth (Scheme 7). Initially, the reaction between chloroheteroarenes and HFIP wherein the proton interacts strongly[28] with the nitrogen atom could be seen as a crucial step in bringing about the possible weakening of the otherwise strong C─Cl bond. Approach of the nucleophile to the electrophilic carbon next to the heteroatom is therefore assisted by the HFIP coordinated complex releasing HCl molecule, eventually leading to the formation of the desired product.

Scheme 7. Plausible Mechanism for HFIP Promoted Thioetherification or Amination of Chloroheteroarenes



CONCLUSION

In conclusion, we have developed a highly efficient and synthetically attractive HFIP promoted thioetherification (aryl and alkylthiols) and amination (secondary amines) of chloroheteroarenes under base-free and metal-free conditions. An attractive feature of the developed protocol is the low temperature conditions (ambient temperature for thioetherification) promoting the functionalisation of temperature sensitive substrates such as 6-chloropurine riboside. With a large substrate scope providing an easy access to synthetically useful molecules, the developed protocol was also found to be highly regioselective in promoting the mono-thioetherification or

amination of dichloroheteroarenes in good to excellent yields. We have also demonstrated the usefulness of the developed synthetic strategy with the synthesis of a Buparilsib intermediate as well as for the modification of a commercially available anti-cancer drug, Ceritinib. A plausible mechanism highlighting the unprecedented promoting effect of HFIP in the given synthetic transformation has also been provided.

EXPERIMENTALSECTION

General Information. All the chemicals and solvents were obtained from commercial sources. All the reactions were performed using oven-dried 20 mL pressure vials. All reactions were monitored by TLC performed on aluminum plates (0.25 mm, E. Merck) precoated with silica gel Merck 60 F-254. Developed TLC plates were visualized under a short wavelength UV lamp. Yields refer to spectroscopically (^{1}H, ^{13}C NMR) homogeneous material obtained after column chromatography. Column chromatography was performed on silica gel (100:200 mesh size) supplied by S. D. Fine Chemicals Limited, India. ^{1}H NMR (400 MHz, 500 MHz) and ^{13}C NMR (101 MHz, 126 MHz) spectra were recorded in $CDCl_3$ and DMSO-d_6 on Agilent 400 MHz and 500 MHz spectrometers. Chemical shifts (δ) are reported in ppm, relative to $SiMe_4$ (δ = 0.0) as an internal standard. The number of protons (*n*) for a given resonance are indicated by *n*H. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublet; ddd, doublet of doublet of doublet; td; triplet of doublet; br; broad. Coupling constant (*J*) values are reported in hertz (Hz). Elemental analysis was performed using an Elementar Vario MICRO cube instrument. High resolution mass spectra were obtained by using positive electrospray ionization (ESI) by time of flight (TOF) method. Melting points were recorded on a standard melting point apparatus and are uncorrected.

General Procedure for Thioetherification of Chloroheteroarenes.A 20 mL oven-dried pressure vial was charged with chloroheteroarene (**1**, 1.0 mmol) and HFIP (1.0 mL). The mixture was stirred at room temperature for 10 min. and to it was added 1.2 equiv. of corresponding thiophenol(**2**,1.2 mmol). The resulting mixture was stirred at room temperature (28 °C) for 12-48 h. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum and the residue obtained was purified by column chromatography on 100:200 mesh silica gel by using ethyl acetate:*n*-hexane (1-15%) solvent system to afford the corresponding products **3a-3q** and **3x-3aa**.In the case of purine derivatives(**3r-3t**) and riboside derivatives (**3u-3w**), MeOH:$CHCl_3$ (1-5%) was used as a mobile phase for column chromatography. Mono thioetherification of polyhalogenated chloroheteroarenes (**6**) was carried out using 1.0 equiv. of corresponding thiophenol(**2**,1.0 mmol) by using above procedure to afford corresponding products **7b**, **7d** and **7f**.

General procedure for amination of chloroheteroarenes.A 20 mL oven-dried pressure vial was charged with chloroheteroarene (**1**,1.0 mmol) and HFIP (1.0 mL). The mixture was stirred at 0 ^{o}C for 10 min. and to it was slowly added 1.2 equiv. of corresponding secondary amine (**4**, 1.2 mmol). The resulting mixture was stirred at 50 °Cin an oil bath for 12 h. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum and the residue obtained was purified by column chromatography on 100:200 mesh silica gel by using ethyl acetate: *n*-hexane (5-10%) solvent system to afford the corresponding products **5a-5s**.In the case of purine derivatives (**5t-5x**) and riboside derivatives (**5y-5ab**), MeOH:$CHCl_3$ (1-5%) was used as a mobile phase for column chromatography.Mono amination of polyhalogenated chloroheteroarenes (**6**) was carried out using 1.0 equiv. of corresponding secondary amine (**4**, 1.0

mmol) by using above procedure to afford corresponding products **7a**, **7c** and **7e**.Diamination of polyhalogenated chloroheteroarenes (**6**) was carried out using 3.0 equiv. of corresponding secondary amine (**4**, 3.0 mmol) by using above procedure to afford corresponding products **8a** and **8b**. Unsymmetrically substituted heteroarenes **9a** and **9b** were obtained by simultaneous mono thioetherification of dichloropyrimidine at room temperature followed by amination of mono thioetherication product at 50 °C by using above procedures.Products **11a** and **11b** were obtained via amination of di and monochloropurine by using Ceritinib (commercially available drug) at 55 °C. Product **11c** was obtained via amination of 2-chlorobenzoxazole by using Norfloxacin methyl ester at 55 °C.

Characterization data of the products

2-(Phenylthio)pyrazine (3a).[29]Yellow oil(177 mg, 94%);Time: 12h; ^{1}H NMR (500 MHz, $CDCl_3$) δ8.34 (dd, *J* = 2.4, 1.6 Hz, 1H), 8.23 (d, *J* = 2.5 Hz, 1H), 8.19 (d, *J* = 1.4 Hz, 1H), 7.63–7.59 (m, 2H), 7.46-7.44 (m, 3H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.7(s, 1C), 143.8 (s, 1C), 142.7 (s, 1C),140.1(s, 1C),135.1 (s, 2C), 129.9 (s, 2C), 129.7 (s, 1C),128.9 (s, 1C).Anal.Calcd (%) for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; N, 14.88; S, 17.03.Found: C, 63.94; H, 4.07; N, 14.96; S, 17.21.

2-((4-Chlorophenyl)thio)pyrazine (3b).[30]Yellow oil(192 mg, 86%); Time: 12h;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 2.5, 1.6 Hz, 1H), 8.27 (distorted t, *J* = 2.9, 2.0 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.1 (s, 1C), 144.2 (s, 1C), 142.4 (s, 1C), 140.0 (s, 1C), 136.3 (s, 2C), 136.2 (s, 1C), 130.1 (s, 2C), 127.2 (s,

1C).Anal.Calcd (%) for $C_{10}H_7ClN_2S$: C, 53.94; H, 3.17; N, 12.58; S, 14.40.Found: C, 53.68; H, 3.39; N, 12.72; S, 14.66.

2-((4-Methoxyphenyl)thio)pyrazine (3c).Yellow oil(195 mg, 89%); Time: 12h;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (dd, *J* = 2.5, 1.6 Hz, 1H), 8.20 (d, *J* = 2.6 Hz, 1H), 8.12 (d, *J* = 1.5 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ161.0 (s, 1C), 159.7 (s, 1C), 143.7 (s, 1C),142.2 (s, 1C), 139.7 (s, 1C), 137.2 (s, 2C), 118.9(s, 1C),115.5 (s, 2C),55.4 (s, 1C). Anal.Calcd (%) for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.73; H, 4.42; N, 12.97; S, 14.91.HRMS (ESI-TOF): *m*/*z* $[M + H]^+$calcd for $C_{11}H_{11}N_2OS$: 219.0592; found: 219.0598.

2-(Pyridin-2-ylthio)pyrazine (3d).[30]Yellow oil(142 mg, 75%); Time: 12h;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 1.3 Hz, 1H), 8.53 (d, *J* = 4.6 Hz, 1H), 8.46 (distorted t, *J* = 2.2, 1.5 Hz, 1H), 8.39 (d, *J* = 2.5 Hz, 1H), 7.66 (td, *J* = 7.7, 1.9 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.21 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.7 (s, 1C), 154.7 (s, 1C), 150.5 (s, 1C), 146.4 (s, 1C), 144.4 (s, 1C), 141.8 (s, 1C), 137.3 (s, 1C), 126.4 (s, 1C), 122.5 (s, 1C).Anal.Calcd (%) for $C_9H_7N_3S$: C, 57.12; H, 3.73; N, 22.21; S, 16.94.Found: C, 57.34; H, 3.91; N, 22.43; S, 16.82.

2-(Phenylthio)quinoxaline (3e).[13c] Off white solid(217 mg, 91%); Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.42 (s, 1H), 7.97 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.70–7.60 (m, 4H), 7.49–7.43 (m, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ157.1 (s, 1C),143.4 (s, 1C), 142.1 (s, 1C), 139.8 (s, 1C),135.0 (s, 2C), 130.4 (s, 1C), 129.8 (s, 2C), 129.6 (s, 1C), 129.1(s,

1C), 128.9 (s, 1C), 128.7 (s, 1C), 128.3 (s, 1C).Anal.Calcd (%) for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.76; S, 13.45. Found: C, 70.72; H, 4.07; N, 11.82; S, 13.53.

2-((4-Chlorophenyl)thio)quinoxaline (3f).White solid(246 mg, 90%); mp 66-68 ^oC; Time: 12h;^1H NMR (500 MHz, $CDCl_3$) δ8.48 (s, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.70–7.62 (m, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H).$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ156.1 (s, 1C), 143.4 (s, 1C), 142.2 (s, 1C), 140.0 (s, 1C), 136.2 (s, 2C), 135.9 (s, 1C), 130.5 (s, 1C), 129.9 (s, 2C), 129.2 (s, 1C), 128.9 (s, 1C), 128.3 (s, 1C), 127.3 (s, 1C).Anal.Calcd (%) for $C_{14}H_9ClN_2S$: C, 61.65; H, 3.33; N, 10.27; S, 11.75. Found: C, 61.83; H, 3.12; N, 10.41; S, 11.63. HRMS (ESI-TOF): m/z $[M + H]^+$calcd for $C_{14}H_{10}ClN_2S$: 273.0253; found: 273.0257.

2-(Pyridin-2-ylthio)quinoxaline (3g).Yellow oil(192mg, 80%); Time: 12h;^1H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.54–8.53 (m, 1H), 8.05 (dd, J = 7.3, 2.4 Hz, 1H), 7.97 (dd, J = 7.8, 1.9 Hz, 1H), 7.75–7.67 (m, 3H), 7.61 (d, J = 8.0 Hz, 1H), 7.25–7.22 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.7 (s, 1C), 153.9 (s, 1C), 150.5 (s, 1C), 146.3 (s, 1C), 142.5 (s, 1C), 140.4 (s, 1C), 137.3 (s, 1C), 130.4 (s, 1C), 129.6 (s, 1C), 129.2 (s, 1C), 128.7 (s, 1C), 126.4 (s, 1C), 122.5 (s, 1C).Anal.Calcd (%) for $C_{13}H_9N_3S$: C, 65.25; H, 3.79; N, 17.56; S, 13.40.Found: C, 65.44; H, 3.97; N, 17.40; S, 13.52.HRMS (ESI-TOF): m/z $[M + H]^+$calcd for $C_{13}H_{10}N_3S$: 240.0595; found: 240.0589.

2-((4-Methoxyphenyl)thio)quinoxaline (3h).Light green solid(239 mg, 89%); mp 63-65 ^oC; Time: 12h;^1H NMR (500 MHz, $CDCl_3$) δ8.37 (s, 1H), 7.97 (dd, J = 8.1, 0.8 Hz, 1H), 7.88 (dd,

J= 8.3, 0.8 Hz, 1H), 7.70–7.67 (m, 1H), 7.63 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H).$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ161.0 (s, 1C), 158.2 (s, 1C),142.9 (s, 1C), 142.1 (s, 1C), 139.7 (s, 1C),137.1 (s, 2C),130.4 (s, 1C), 129.1 (s, 1C), 128.5 (s, 1C), 128.2 (s, 1C), 118.9 (s, 1C),115.5 (s, 2C), 55.5 (s, 1C).Anal.Calcd (%) for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.32; H, 4.39; N, 10.56; S, 11.83.HRMS (ESI-TOF): *m*/*z* $[M + H]^+$calcd for $C_{15}H_{13}N_2OS$: 269.0749; found: 269.0755.

2-((1-Methyl-1H-tetrazol-5-yl)thio)quinoxaline (3i).Pale yellow solid(208 mg, 85%); mp 158-160 °C; Time: 12h;^{1}H NMR (500 MHz, $CDCl_3$) δ8.82 (s, 1H), 8.09–8.05 (m, 1H), 7.79–7.71 (m, 3H), 4.15 (s, 3H).$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 149.8 (s, 1C), 147.2 (s, 1C), 142.9 (s, 1C), 142.3 (s, 1C), 140.8 (s, 1C), 131.3 (s, 1C), 130.3 (s, 1C), 129.4 (s, 1C), 128.3 (s, 1C), 34.8 (s, 1C).Anal.Calcd (%) for $C_{10}H_8N_6S$: C, 49.17; H, 3.30; N, 34.40; S, 13.12.Found: C, 49.35; H, 3.09; N, 34.58; S, 13.20. HRMS (ESI-TOF): *m*/*z* $[M + H]^+$calcd for $C_{10}H_9N_6S$: 245.0609; found: 245.0613.

2-(Naphthalen-1-ylthio)quinoxaline (3j).Off white solid(272 mg, 94%); mp 120-122 °C; Time: 12h;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.2 Hz, 1H), 8.14 (s, 1H), 8.02 (distorted t, *J* = 8.5, 7.1 Hz, 2H), 7.94 (dd, *J* = 8.1, 3.9 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.69–7.66 (m, 1H), 7.63–7.60 (m, 1H), 7.58–7.50 (m, 3H).$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 157.5 (s, 1C), 142.8 (s, 1C), 142.1 (s, 1C), 139.7 (s, 1C), 135.8 (s, 1C), 134.6 (s, 1C), 134.5 (s, 1C), 131.4 (s, 1C), 130.5 (s, 1C), 129.1 (s, 1C), 128.8 (s, 1C), 128.7 (s, 1C), 128.2 (s, 1C), 127.7 (s, 1C), 126.8 (s, 1C), 126.0 (s, 1C), 125.7 (s, 1C), 125.6 (s, 1C).Anal.Calcd (%) for $C_{18}H_{12}N_2S$: C, 74.97; H, 4.19;

N, 9.71; S, 11.12.Found: C, 74.73; H, 4.07; N, 9.63; S, 11.22. HRMS (ESI-TOF): *m/z* [M + H]$^+$calcd for $C_{18}H_{13}N_2S$: 289.0799; found: 289.0791.

Methyl 2-(quinoxalin-2-ylthio)benzoate (3k).[30]White solid(255 mg, 86%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.00 (distorted t, *J* = 9.2, 8.7 Hz, 2H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.71–7.64 (m, 2H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.49–7.42 (m, 2H), 3.80 (s, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9 (s, 1C), 155.7 (s, 1C), 145.1 (s, 1C), 142.3 (s, 1C), 140.2 (s, 1C), 134.4 (s, 1C), 133.4 (s, 1C), 132.3 (s, 1C), 131.8 (s, 1C), 131.1 (s, 1C), 130.4 (s, 1C), 129.1 (s, 1C), 129.1 (s, 1C), 128.5 (s, 1C), 128.4 (s, 1C), 52.3 (s, 1C).Anal.Calcd (%) for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45; S, 10.82.Found: C, 64.97; H, 4.03; N, 9.62; S, 10.78.

2-((4-Fluorophenyl)thio)quinoxaline (3l).White solid(223 mg, 87%); mp 50-52 ^{o}C; Time: 12h;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.99 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.70–7.62 (m, 4H), 7.20–7.15 (m, 2H).^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.7 (d, $J_{C,F}$ = 251.4 Hz, 1C), 156.7 (s, 1C), 143.1 (s, 1C), 142.2 (s, 1C), 139.9 (s, 1C), 137.4 (d, $J_{C,F}$ = 8.6 Hz, 2C), 130.5 (s, 1C), 129.2 (s, 1C), 128.8 (s, 1C), 128.2 (s, 1C), 123.8 (d, $J_{C,F}$ = 3.4 Hz, 1C), 117.0 (d, $J_{C,F}$ = 22.2 Hz, 2C).Anal.Calcd (%) for $C_{14}H_9FN_2S$: C, 65.61; H, 3.54; N, 10.93; S, 12.51.Found: C, 65.79; H, 3.68; N, 10.78; S, 12.70. HRMS (ESI-TOF): *m/z* [M + H]$^+$calcd for $C_{14}H_{10}FN_2S$: 257.0549; found: 257.0545.

2-(Phenylthio)benzo[d]thiazole (3m).[31]Yellow oil(212 mg, 87%); Time: 48h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 6.6 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.53–7.45 (m, 3H), 7.39 (distorted t, *J* = 8.0, 7.4 Hz, 1H), 7.26 (distorted t, *J* = 8.0, 6.8 Hz,

1H).$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.6(s, 1C), 153.9 (s, 1C),135.5 (s, 1C),135.3 (s, 2C),130.4 (s, 1C),130.0 (s, 1C),129.9 (s, 2C),126.1 (s, 1C), 124.3 (s, 1C), 121.9 (s, 1C), 120.8 (s, 1C).Anal.Calcd (%) for $C_{13}H_9NS_2$: C, 64.17; H, 3.73; N, 5.76; S, 26.35. Found: C, 64.33; H, 3.61; N, 5.90; S, 26.47.

2-((1-Methyl-1H-tetrazol-5-yl)thio)benzo[d]thiazole (3n). White solid(197 mg, 79%); mp 96-98 ^oC; Time: 48h;^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.46 (distorted t, J = 8.2, 7.2 Hz, 1H), 7.39 (distorted t, J = 8.0, 7.2 Hz, 1H), 4.16 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.4 (s, 1C), 152.7 (s, 1C), 147.8 (s, 1C), 136.2(s, 1C), 126.8 (s, 1C), 125.9 (s, 1C), 122.9 (s, 1C), 121.3 (s, 1C), 34.8 (s, 1C).Anal.Calcd (%) for $C_9H_7N_5S_2$: C, 43.36; H, 2.83; N, 28.09; S, 25.72. Found: C, 43.50; H, 2.70; N, 28.26; S, 25.84.HRMS (ESI-TOF): m/z $[M + H]^+$calcd for $C_9H_8N_5S_2$: 250.0221; found: 250.0229.

2-((4-Methoxyphenyl)thio)benzo[d]thiazole (3o).[31] White solid(222 mg, 81%);Time: 48h;^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.9 Hz, 2H), 7.62 (d, J = 8.7 Hz, 1H), 7.38 (t, J = 7.1 Hz, 1H), 7.23 (distorted t, J = 7.3, 6.7 Hz, 1H), 6.99 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H).$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.8 (s, 1C), 161.7 (s, 1C), 154.2 (s, 1C),137.5 (s, 2C),135.4 (s, 1C), 126.0 (s, 1C), 124.0 (s, 1C), 121.7 (s, 1C), 120.7 (s, 1C), 120.2 (s, 1C), 115.5 (s, 2C), 55.4 (s, 1C).Anal.Calcd (%) for $C_{14}H_{11}NOS_2$: C, 61.51; H, 4.06; N, 5.12; S, 23.46. Found: C, 61.63; H, 4.02; N, 5.26; S, 23.60.

2-((4-Chlorophenyl)thio)benzo[d]thiazole (3p).[32] White solid(231 mg, 83%); Time: 48h;^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 1H), 7.66 (distorted t, J = 8.5, 6.3 Hz, 3H), 7.44

(d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 8.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 168.2 (s, 1C), 153.8 (s, 1C), 136.9 (s, 1C), 136.4 (s, 2C), 135.6 (s, 1C), 130.1 (s, 2C), 128.4 (s, 1C), 126.3 (s, 1C), 124.5 (s, 1C), 122.1 (s, 1C), 120.8 (s, 1C).Anal.Calcd (%) for $C_{13}H_8ClNS_2$: C, 56.21; H, 2.90; N, 5.04; S, 23.08. Found: C, 56.37; H, 2.74; N, 5.16; S, 23.20.

2-(Naphthalen-1-ylthio)benzo[d]thiazole (3q).[33]White solid(235 mg, 80%); Time: 48h;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52–8.43 (m, 1H), 8.06 (d, *J* = 7.6 Hz, 2H), 7.96–7.90 (m, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.61–7.53 (m, 3H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.37 (distorted t, *J* = 8.0, 7.4 Hz, 1H), 7.20 (distorted t, *J* = 7.9, 7.3 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 170.0 (s, 1C), 153.9 (s, 1C), 136.3 (s, 1C), 135.6 (s, 1C), 134.5 (s, 1C), 134.3 (s, 1C), 132.1 (s, 1C), 128.8 (s, 1C), 127.9 (s, 1C), 126.9 (s, 1C), 126.9 (s, 1C), 126.1 (s, 1C), 125.9 (s, 1C), 125.5 (s, 1C), 124.1 (s, 1C), 121.8 (s, 1C), 120.7 (s, 1C). Anal.Calcd (%) for $C_{17}H_{11}NS_2$: C, 69.59; H, 3.78; N, 4.77; S, 21.85. Found: C, 69.73; H, 3.62; N, 4.61; S, 21.95.

6-(Phenylthio)-9H-purine (3r).[34]White solid(162 mg, 71%); Time: 12h;^{1}H NMR (500 MHz, DMSO-d_6) δ 13.59 (s, 1H), 8.52 (s, 1H), 8.49 (s, 1H), 7.63–7.60 (m, 2H), 7.49–7.46 (m, 3H).$^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 158.5 (s, 1C), 152.1 (s, 1C), 150.1 (s, 1C), 143.9 (s, 1C),135.9 (s, 2C),130.1 (s, 1C), 129.9 (s, 2C), 129.8(s, 1C), 127.4 (s, 1C).Anal.Calcd (%) for $C_{11}H_8N_4S$: C, 57.88; H, 3.53; N, 24.54; S, 14.04. Found: C, 57.96; H, 3.39; N, 24.68; S, 14.18.

6-((4-Chlorophenyl)thio)-9H-purine (3s).[35]White solid(171 mg, 65%);Time: 12h;^{1}H NMR (500 MHz, DMSO-d_6) δ13.61 (s, 1H), 8.54 (s, 1H), 8.50 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H).$^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 157.8 (s, 1C), 152.0 (s, 1C), 150.1(s, 1C),

144.1 (s, 1C), 137.6 (s, 2C), 135.0 (s, 1C), 129.9 (s, 1C), 129.8 (s, 2C), 126.5 (s, 1C).Anal.Calcd (%) for $C_{11}H_7ClN_4S$: C, 50.29; H, 2.69; N, 21.33; S, 12.20. Found: C, 50.44; H, 2.56; N, 21.45; S, 12.36.

6-((4-Methoxyphenyl)thio)-9H-purine (3t).[35]White solid(173 mg, 67%); Time: 12h;^{1}H NMR (500 MHz, DMSO-d_6) δ 13.54 (s, 1H), 8.50 (s, 1H), 8.46 (s, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.9 (s, 1C), 159.2 (s, 1C), 152.1 (s, 1C), 149.9 (s, 1C), 143.8 (s, 1C), 137.8 (s, 2C), 130.0 (s, 1C), 117.4 (s, 1C), 115.5 (s, 2C), 55.8 (s, 1C).Anal.Calcd (%) for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69; S, 12.41. Found: C, 55.94; H, 3.78; N, 21.80; S, 12.55.

(2R,3S,4R,5R)-2-(Hydroxymethyl)-5-(6-((4-methoxyphenyl)thio)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (3u).White solid(262 mg, 67%); mp 74-76 ^{o}C; Time: 18h;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.54 (s, 1H), 7.50 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.7 Hz, 2H), 5.96 (d, J = 5.4 Hz, 1H), 5.48 (d, J = 5.9 Hz, 1H), 5.19 (d, J = 4.9 Hz, 1H), 5.07 (t, J = 5.4 Hz, 1H), 4.57 (dd, J = 10.5, 5.3 Hz, 1H), 4.16 (t, J = 4.1 Hz, 1H), 3.94 (d, J = 3.4 Hz, 1H), 3.80 (s, 3H), 3.71–3.62 (m, 1H), 3.60–3.50 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.0 (s, 1C), 160.4 (s, 1C), 152.1 (s, 1C), 148.9 (s, 1C), 144.0 (s, 1C), 137.8 (s, 2C), 130. 9 (s, 1C), 117.2 (s, 1C), 115.5 (s, 2C),88.3 (s, 1C), 86.1 (s, 1C), 74.2 (s, 1C), 70.7 (s, 1C), 61.7 (s, 1C), 55.8 (s, 1C).Anal.Calcd (%) for $C_{17}H_{18}N_4O_5S$: C, 52.30; H, 4.65; N, 14.35; S, 8.21. Found: C, 52.42; H, 4.47; N, 14.49; S, 8.35. HRMS (ESI-TOF): m/z [M + H]$^+$calcd for $C_{17}H_{19}N_4O_5S$: 391.1076;found: 391.1084.

(2R,3R,4S,5R)-2-(6-((4-Fluorophenyl)thio)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (3v). White solid(224 mg, 59%); mp 64-66 °C; Time: 18h;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.57 (s, 1H), 7.66 (dd, J = 8.4, 5.5 Hz, 2H), 7.33 (t, J = 8.7 Hz, 2H), 5.97 (d, J = 5.4 Hz, 1H), 5.49 (d, J = 5.8 Hz, 1H), 5.19 (d, J = 5.0 Hz, 1H), 5.06 (t, J = 5.4 Hz, 1H), 4.57 (dd, J = 10.7, 5.4 Hz, 1H), 4.15 (dd, J = 8.3, 4.3 Hz, 1H), 3.95 (d, J = 3.6 Hz, 1H), 3.70–3.62 (m, 1H), 3.58–3.51 (m, 1H).^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 163.5 (d, $J_{C,F}$ = 249.5 Hz, 1C), 159.4(s, 1C), 152.1 (s, 1C),149.1 (s, 1C), 144.2 (s, 1C),138.5 (d, $J_{C,F}$ = 9.1 Hz, 2C),131.0 (s, 1C),122.7 (d, $J_{C,F}$ = 3.0 Hz, 1C),117.0 (d, $J_{C,F}$ = 22.2 Hz, 2C),88.3 (s, 1C), 86.1 (s, 1C), 74.2 (s, 1C), 70.7 (s, 1C), 61.6 (s, 1C).Anal.Calcd (%) for $C_{16}H_{15}FN_4O_4S$: C, 50.79; H, 4.00; N, 14.81; S, 8.47. Found: C, 50.91; H, 3.87; N, 14.73; S, 8.34. HRMS (ESI-TOF): m/z [M + H]$^{+}$calcd for $C_{16}H_{16}FN_4O_4S$: 379.0876; found: 379.0882.

(2R,3S,4R,5R)-2-(Hydroxymethyl)-5-(6-(phenylthio)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (3w).[30] White solid(256 mg, 71%); Time: 18h;^{1}H NMR (400 MHz, DMSO-d_6) δ8.74 (s, 1H), 8.56 (s, 1H), 7.65–7.56 (m, 2H), 7.52–7.42 (m, 3H), 5.97 (d, J = 5.4 Hz, 1H), 5.50 (d, J = 5.9 Hz, 1H), 5.21 (d, J = 4.9 Hz, 1H), 5.09 (t, J = 5.4 Hz, 1H), 4.58 (dd, J = 10.6, 5.3 Hz, 1H), 4.16 (dd, J = 8.2, 4.6 Hz, 1H), 3.95 (d, J = 3.5 Hz, 1H), 3.70–3.63 (m, 1H), 3.59–3.51 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 159.5 (s, 1C), 152.1 (s, 1C), 149.1 (s, 1C), 144.2 (s, 1C),135.9 (s, 2C), 131.0 (s, 1C), 130.0 (s, 1C), 129.8 (s, 2C), 127.1 (s, 1C), 88.3 (s, 1C), 86.1 (s, 1C), 74.2 (s, 1C), 70.7 (s, 1C), 61.6 (s, 1C).Anal.Calcd (%) for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.48; N, 15.55; S, 8.90. Found: C, 53.51; H, 4.32; N, 15.47; S, 8.71.

2-(Decylthio)quinoxaline (3x).White solid(288 mg, 95%); mp 88-90 °C; Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 3.32 (t, *J* = 7.3 Hz, 2H), 1.81–1.73 (m, 2H), 1.51–1.44 (m, 2H), 1.36–1.24 (m, 12H), 0.86 (t, *J* = 6.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.5 (s, 1C), 144.9 (s, 1C), 142.8 (s, 1C), 139.7 (s, 1C), 130.0 (s, 1C), 129.2 (s, 1C), 127.8 (s, 1C), 127.8 (s, 1C), 31.9 (s, 1C), 29.6 (s, 1C), 29.6 (s, 1C), 29.5 (s, 1C), 29.3 (s, 1C), 29.1 (s, 1C), 29.0 (s, 1C), 28.9 (s, 1C), 22.6 (s, 1C), 14.1 (s, 1C).Anal.Calcd (%) for $C_{18}H_{26}N_2S$: C, 71.48; H, 8.66; N, 9.26; S, 10.60.Found: C, 71.56; H, 8.84; N, 9.38; S, 10.48.HRMS (ESI-TOF): *m*/*z* $[M + H]^+$calcd for $C_{18}H_{27}N_2S$: 303.1895; found: 303.1887.

2-((2-Chlorobenzyl)thio)quinoxaline (3y).White solid(267 mg, 93%); mp 52-54 °C; Time: 12h;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.01 (dd, *J* = 7.8, 5.4 Hz, 2H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.66–7.62 (m, 2H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.21–7.16 (m, 2H), 4.72 (s, 2H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ155.3 (s, 1C), 144.6 (s, 1C), 142.5 (s, 1C), 140.0 (s, 1C), 135.2 (s, 1C), 134.5 (s, 1C), 131.3 (s, 1C), 130.3 (s, 1C), 129.6 (s, 1C), 129.3 (s, 1C), 128.9 (s, 1C), 128.1 (s, 1C), 127.8 (s, 1C), 126.8 (s, 1C), 31.2 (s, 1C).Anal.Calcd(%) for $C_{15}H_{11}ClN_2S$: C, 62.82; H, 3.87; N, 9.77; S, 11.18. Found: C, 62.90; H, 3.71; N, 9.60; S, 11.36. HRMS (ESI-TOF): *m*/*z* $[M + H]^+$calcd for $C_{15}H_{12}ClN_2S$: 287.0410; found: 287.0416.

2-(Cyclohexylthio)quinoxaline (3z).Off white solid(225 mg, 92%); mp 54-56 °C; Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.58 (t, *J* = 6.9 Hz, 1H), 4.13–4.05 (m, 1H), 2.20–2.10 (m, 2H), 1.79 (dd, *J* = 8.7, 3.8 Hz, 2H), 1.67–1.49 (m, 5H), 1.40–1.31 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz,$CDCl_3$) δ

156.4 (s, 1C), 145.1 (s, 1C), 142.8 (s, 1C), 139.7 (s, 1C), 129.9 (s, 1C), 129.2 (s, 1C), 127.8 (s, 1C), 127.8 (s, 1C),42.7 (s, 1C),32.9 (s, 2C),25.9 (s, 1C),25.7 (s, 2C).Anal.Calcd (%) for $C_{14}H_{16}N_2S$: C, 68.82; H, 6.60; N, 11.46; S, 13.12. Found: C, 68.92; H, 6.44; N, 11.30; S, 13.26. HRMS (ESI-TOF): *m*/*z* $[M + H]^+$calcdfor $C_{14}H_{17}N_2S$: 245.1112; found: 245.1120.

2-(Phenylthio)benzo[d]oxazole (3aa).[31]Colorless oil(196 mg, 86%); Time: 12h; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 5.8, 2.9 Hz, 2H), 7.59 (dd, *J*= 6.0, 1.6 Hz, 1H), 7.50–7.38 (m, 4H), 7.27–7.21 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.3 (s, 1C), 151.8 (s, 1C), 141.9 (s, 1C),134.4 (s, 2C), 129.8 (s, 1C), 129.6 (s, 2C), 127.2 (s, 1C), 124.3 (s, 1C), 124.3 (s, 1C), 119.1 (s, 1C), 110.0 (s, 1C).Anal.Calcd (%) for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16; S, 14.11. Found: C, 68.82; H, 3.95; N, 6.30; S, 14.21.

N,N-Diethylbenzo[d]oxazol-2-amine (5a).[36]Yellow oil(153 mg, 80%);Time: 12h;^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.12 (td, *J* = 7.6, 0.9 Hz, 1H), 6.95 (td, *J* = 7.8, 1.0 Hz, 1H), 3.56 (q, *J* = 7.1 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 6H).$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.2 (s, 1C), 148.8 (s, 1C), 143.6 (s, 1C), 123.7 (s, 1C), 119.9 (s, 1C), 115.8 (s, 1C), 108.4 (s, 1C), 42.9 (s, 2C), 13.4 (s, 2C). Anal.Calcd (%) for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.57; H, 7.50; N, 14.81.

N-Benzyl-N-methylbenzo[d]oxazol-2-amine (5b).[37]Off white solid(189 mg, 79%); Time: 12h;^1H NMR (400 MHz, $CDCl_3$) δ7.42–7.21 (m, 7H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 1H), 4.75 (s, 2H), 3.12 (s, 3H).$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ163.0 (s, 1C), 149.0 (s, 1C), 143.5 (s, 1C), 136.4 (s, 1C), 128.7 (s, 2C), 127.7 (s, 1C), 127.6 (s, 2C), 123.9 (s, 1C), 120.3 (s, 1C),

116.1 (s, 1C), 108.7 (s, 1C), 53.8 (s, 1C), 35.1 (s, 1C).Anal.Calcd (%) for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.73; H, 5.98; N, 11.86.

2-(Azetidin-1-yl)benzo[d]oxazole (5c). White solid(121 mg, 69%); mp 88-90°C; Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ7.35 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 1H), 4.26 (t, *J* = 7.6 Hz, 4H), 2.50–2.43 (m, 2H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ162.7 (s, 1C), 149.1 (s, 1C), 143.1 (s, 1C), 123.9 (s, 1C), 120.7 (s, 1C), 116.5 (s, 1C), 108.8 (s, 1C), 51.4 (s, 2C), 17.4 (s, 1C).Anal.Calcd (%) for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.87; H, 5.91; N, 16.20.HRMS (ESI-TOF): *m*/*z* [M + H]$^+$calcd for $C_{10}H_{11}N_2O$: 175.0871; found: 175.0877.

2-(Pyrrolidin-1-yl)benzo[d]oxazole (5d).[37] White solid(153 mg, 81%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ7.33 (d, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 3.62 (t, *J* = 6.5 Hz, 4H), 2.00 (t, *J* = 6.5 Hz, 4H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.0 (s, 1C), 149.0 (s, 1C), 143.6 (s, 1C), 123.7 (s, 1C), 120.0 (s, 1C), 115.9 (s, 1C), 108.5 (s, 1C), 47.4 (s, 2C), 25.5 (s, 2C).Anal.Calcd (%) for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88.Found: C, 70.31; H, 6.30; N, 14.96.

2-(3-Methylpiperidin-1-yl)benzo[d]oxazole (5e).[38] White solid(180 mg, 83%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ7.31 (d, *J* = 7.7 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.96 (t, *J* = 7.7 Hz, 1H), 4.16 (t, *J* = 11.4 Hz, 2H), 3.00 (td, *J* = 12.6, 2.9 Hz, 1H), 2.68 (dd, *J* = 12.6, 11.0 Hz, 1H), 1.83 (d, *J* = 12.0 Hz, 1H), 1.78–1.68 (m, 2H), 1.65–1.54 (m, 1H), 1.18–1.08 (m, 1H), 0.94 (d, *J* = 6.6 Hz, 3H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.3 (s, 1C), 148.6

(s, 1C), 143.3 (s, 1C), 123.8 (s, 1C), 120.2 (s, 1C), 115.9 (s, 1C), 108.5 (s, 1C), 53.0 (s, 1C), 46.0 (s, 1C), 32.6 (s, 1C), 30.6 (s, 1C), 24.7 (s, 1C), 18.9 (s, 1C). Anal.Calcd (%) for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.33; H, 7.36; N, 12.83.

2-(4-(2-Methoxyphenyl)piperazin-1-yl)benzo[d]oxazole (5f).[39]White solid(267 mg, 86%);Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.05–6.99 (m, 2H), 6.97–6.92 (m, 2H), 6.88 (d, *J* = 7.9 Hz, 1H), 3.87 (distorted d, *J* = 7.1 Hz, 7H), 3.16 (t, *J* = 4.9 Hz, 4H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.2 (s, 1C), 152.3 (s, 1C), 148.8 (s, 1C), 143.1 (s, 1C), 140.8 (s, 1C), 124.0 (s, 1C), 123.6 (s, 1C), 121.1 (s, 1C), 120.6 (s, 1C), 118.5 (s, 1C), 116.3 (s, 1C), 111.4 (s, 1C), 108.7 (s, 1C), 55.5 (s, 1C), 50.2 (s, 2C), 45.9 (s, 2C). Anal.Calcd (%) for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58.Found: C, 69.96; H, 6.31; N, 13.70.

2-(Azepan-1-yl)benzo[d]oxazole (5g).[37]Off white solid(160 mg, 74%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.7 Hz, 1H), 3.68 (t, *J* = 5.8 Hz, 4H), 1.82 (br s, 4H), 1.59 (br s, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.6 (s, 1C), 148.8 (s, 1C), 143.7 (s, 1C), 123.7 (s, 1C), 119.8 (s, 1C), 115.7 (s, 1C), 108.4 (s, 1C), 48.0 (s, 2C), 28.2 (s, 2C), 27.4 (s, 2C). Anal.Calcd (%) for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.34; H, 7.32; N, 12.81.

2-(Azetidin-1-yl)benzo[d]thiazole (5h).Pale yellow solid(82 mg, 43%); mp 96-98 ^{o}C; Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 4.18 (t, *J* = 7.4 Hz, 4H), 2.51–2.43 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ

168.4 (s, 1C), 153.0 (s, 1C), 131.4 (s, 1C), 125.9 (s, 1C), 121.3 (s, 1C), 120.9 (s, 1C), 119.1 (s, 1C), 53.0 (s, 2C), 17.4 (s, 1C). Anal.Calcd (%) for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; S, 16.85. Found: C, 63.27; H, 5.44; N, 14.59; S, 16.93. HRMS (ESI-TOF): *m*/*z* $[M + H]^+$calcd for $C_{10}H_{11}N_2S$: 191.0643; found: 191.0651.

2-(Pyrrolidin-1-yl)benzo[d]thiazole (5i).[40]Pale yellow solid(98 mg, 48%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ7.56 (d, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 7.9 Hz, 1H), 7.02 (t, *J* = 7.9 Hz, 1H), 3.56 (t, *J* = 6.4 Hz, 4H), 2.05 (t, *J* = 6.7 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.3 (s, 1C), 153.3 (s, 1C), 130.7 (s, 1C), 125.8 (s, 1C), 120.6 (s, 2C), 118.6 (s, 1C), 49.4 (s, 2C), 25.6 (s, 2C). Anal.Calcd (%) for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71; S, 15.69. Found: C, 64.83; H, 5.80; N, 13.85; S, 15.81.

2-(Piperidin-1-yl)benzo[d]thiazole (5j).[41]White solid(90 mg, 41%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 3.59 (br s, 4H), 1.68 (br s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.9 (s, 1C), 152.9 (s, 1C), 130.6 (s, 1C), 125.8 (s, 1C), 121.0 (s, 1C), 120.5 (s, 1C), 118.8 (s, 1C), 49.6 (s, 2C), 25.3 (s, 2C), 24.2 (s, 1C). Anal.Calcd (%) for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83; S, 14.69. Found: C, 66.20; H, 6.30; N, 12.68; S, 14.61.

4-(Benzo[d]thiazol-2-yl)morpholine (5k).[41]White solid(80 mg, 36%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 3.82 (t, *J* = 4.8 Hz, 4H), 3.61 (t, *J* = 4.8 Hz, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 169.0 (s, 1C), 152.5 (s, 1C), 130.6 (s, 1C), 126.1 (s, 1C), 121.6 (s, 1C), 120.7 (s, 1C),

119.3 (s, 1C), 66.2 (s, 2C), 48.5 (s, 2C).Anal.Calcd (%) for $C_{11}H_{12}N_2OS$: C, 59.98; H, 5.49; N, 12.72; S, 14.55. Found: C, 59.86; H, 5.33; N, 12.80; S, 14.67.

2-(4-(2-Methoxyphenyl)piperazin-1-yl)benzo[d]thiazole (5l).[39]Off white solid(160 mg, 49%); Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.11–6.99 (m, 2H), 6.97–6.91 (m, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.88 (s, 3H), 3.81 (t, *J* = 4.7 Hz, 4H), 3.18 (t, *J* = 4.7 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.8 (s, 1C), 152.7 (s, 1C), 152.3 (s, 1C), 140.7 (s, 1C), 130.7 (s, 1C), 126.0 (s, 1C), 123.6 (s, 1C), 121.4 (s, 1C), 121.1 (s, 1C), 120.7 (s, 1C), 119.1 (s, 1C), 118.5 (s, 1C), 111.4 (s, 1C), 55.5 (s, 1C), 50.2 (s, 2C), 48.7 (s, 2C). Anal.Calcd (%) for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.89; N, 12.91; S, 9.85.Found: C, 66.59; H, 5.75; N, 12.77; S, 9.95.

2-(Azepan-1-yl)benzo[d]thiazole (5m).[42]Pale yellow oil(105 mg, 45%); Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.25 (t, *J* = 8.1 Hz, 1H), 7.00 (t, *J* = 7.9 Hz, 1H), 3.66 (t, *J* = 5.5 Hz, 4H), 1.84 (br s, 4H), 1.60 (d, *J* = 2.9 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.0 (s, 1C), 153.3 (s, 1C), 130.5 (s, 1C), 125.8 (s, 1C), 120.6 (s, 1C), 120.4 (s, 1C), 118.5 (s, 1C), 50.8 (s, 2C), 27.9 (s, 2C), 27.5 (s, 2C).Anal.Calcd (%) for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06; S, 13.80. Found: C, 67.30; H, 6.80; N, 12.18; S, 13.94.

2-(Azetidin-1-yl)pyrimidine (5n).[13b]Pale yellow oil(80 mg, 59%); Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.8 Hz, 2H), 6.46 (t, *J* = 4.7 Hz, 1H), 4.12 (t, *J* = 7.5 Hz, 4H), 2.38–2.31 (m, 2H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.5 (s, 1C), 157.8 (s, 2C), 109.7 (s, 1C),

50.0 (s, 2C), 16.2 (s, 1C). Anal.Calcd (%) for $C_7H_9N_3$: C, 62.20; H, 6.71; N, 31.09. Found: C, 62.34; H, 6.58; N, 31.20.

2-(Pyrrolidin-1-yl)pyrimidine (5o).[13b]Pale yellow oil(109 mg, 73%); Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 4.7 Hz, 2H), 6.41 (t, *J* = 4.7 Hz, 1H), 3.54 (t, *J* = 6.6 Hz, 4H), 1.97 (t, *J* = 6.6 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.2 (s, 1C), 157.6 (s, 2C), 108.8 (s, 1C), 46.5 (s, 2C), 25.5 (s, 2C). Anal.Calcd (%) for $C_8H_{11}N_3$: C,64.40; H, 7.43; N, 28.16. Found: C, 64.56; H, 7.35; N, 28.30.

2-(Piperidin-1-yl)pyrimidine (5p).[43]Pale yellow oil(128 mg, 78%); Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.7 Hz, 2H), 6.39 (t, *J* = 4.7 Hz, 1H), 3.75 (t, *J* = 5.1 Hz, 4H), 1.65–1.58 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7 (s, 1C), 157.6 (s, 2C), 109.0 (s, 1C), 44.7 (s, 2C), 25.7 (s, 2C), 24.8 (s, 1C). Anal.Calcd (%) for $C_9H_{13}N_3$: C, 66.23; H, 8.03; N, 25.74. Found: C, 66.37; H, 8.15; N, 25.82.

2-(4-(2-Methoxyphenyl)piperazin-1-yl)pyrimidine (5q).[44]Off white solid(206 mg, 76%); Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.7 Hz, 2H), 7.00 (td, *J* = 8.0, 2.3 Hz, 1H), 6.96–6.90 (m, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.47 (t, *J* = 4.7 Hz, 1H), 3.99 (t, *J* = 4.9 Hz, 4H), 3.88 (s, 3H), 3.10 (t, *J* = 4.9 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.7 (s, 1C), 157.7 (s, 2C), 152.3 (s, 1C), 141.3 (s, 1C), 123.2 (s, 1C), 121.0 (s, 1C), 118.4 (s, 1C), 111.3 (s, 1C), 109.8 (s, 1C), 55.4 (s, 1C), 50.7 (s, 2C), 44.0 (s, 2C). Anal.Calcd (%) for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.76; H, 6.59; N, 20.85.

1-(Pyrimidin-2-yl)azepane (5r).[13b]Pale yellow oil(121 mg, 68%); Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 4.7 Hz, 2H), 6.39 (t, *J* = 4.7 Hz, 1H), 3.72 (t, *J* = 5.9 Hz, 4H), 1.76 (br s, 4H), 1.54 (d, *J* = 3.0 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.5 (s, 1C), 157.6 (s, 2C), 108.7 (s, 1C), 46.9 (s, 2C), 27.8 (s, 2C), 27.3 (s, 2C). Anal.Calcd (%) for $C_{10}H_{15}N_3$: C, 67.76; H, 8.53; N, 23.71. Found: C, 67.90; H, 8.45; N, 23.83.

5-Nitro-2-(piperidin-1-yl)pyridine (5s).[45]Yellow solid(119 mg, 57%); Time: 12h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, *J* = 2.5 Hz, 1H), 8.13 (dd, *J* = 9.6, 2.8 Hz, 1H), 6.52 (d, *J* = 9.6 Hz, 1H), 3.72 (t, *J* = 5.3 Hz, 4H), 1.71–1.61 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.2 (s, 1C), 146.7 (s, 1C), 134.3 (s, 1C), 132.8 (s, 1C), 104.3 (s, 1C), 46.2 (s, 2C), 25.6 (s, 2C), 24.4 (s, 1C).Anal.Calcd (%) for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.80; H, 6.46; N, 20.40.

6-(Pyrrolidin-1-yl)-9H-purine (5t).[46]White solid(120 mg, 63%); Time: 12h;^{1}H NMR (400 MHz, DMSO-d_6) δ 12.84 (br s, 1H), 8.12 (s, 1H), 8.00 (s, 1H), 4.00 (br s, 2H), 3.59 (br s, 2H), 1.90 (br s, 4H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 152.9 (s, 1C), 152.6 (s, 1C), 151.0 (s, 1C), 138.5 (s, 1C), 119.5 (s, 1C), 47.5 (s, 2C), 26.2 (s, 2C). Anal.Calcd (%) for $C_9H_{11}N_5$: C, 57.13; H, 5.86; N, 37.01. Found: C, 57.27; H, 5.76; N, 37.13.

6-(Piperidin-1-yl)-9H-purine (5u).[47]White solid(153 mg, 75%); Time: 12h;^{1}H NMR (500 MHz, DMSO-d_6) δ 12.96 (br s, 1H), 8.15 (s, 1H), 8.06 (s, 1H), 4.17 (br s, 4H), 1.68–1.62 (m, 2H), 1.56–1.52 (m, 4H).^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ153.5 (s, 1C), 152.3 (s, 1C),151.7 (s,

1C), 138.2 (s, 1C), 119.1 (s, 1C),46.1 (s, 2C), 26.1 (s, 2C), 24.8 (s, 1C).Anal.Calcd (%) for $C_{10}H_{13}N_5$: C, 59.10; H, 6.45; N, 34.46. Found: C, 59.24; H, 6.29; N, 34.54.

4-(9H-Purin-6-yl)morpholine (5v).[48]White solid(158 mg, 77%); Time: 12h;^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (br s, 1H), 8.19 (s, 1H), 8.10 (s, 1H), 4.17 (br s, 4H), 3.68 (t, J = 4.5 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 153.6 (s, 1C), 152.2 (s, 1C), 151.9 (s, 1C), 138.7 (s, 1C), 119.3 (s, 1C), 66.6 (s, 2C), 45.6 (s, 2C).Anal.Calcd (%) for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.79; H, 5.28; N, 34.25.

tert-Butyl 4-(9H-purin-6-yl)piperazine-1-carboxylate (5w).[12e]White solid(217 mg, 71%); Time: 12h;^{1}H NMR (400 MHz, DMSO-d_6) δ13.03 (br s, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 4.17 (br s, 4H), 3.42 (br s, 4H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 154.3 (s, 1C), 153.5 (s, 1C), 152.2 (s, 1C), 151.9 (s, 1C), 138.8 (s, 1C), 119.3 (s, 1C), 79.6 (s, 1C), 44.8 (s, 2C), 44.0(s, 2C), 28.5 (s, 3C).Anal.Calcd (%) for $C_{14}H_{20}N_6O_2$: C, 55.25; H, 6.62; N, 27.61. Found: C, 55.37; H, 6.48; N, 27.70.

6-(Azepan-1-yl)-9H-purine (5x).[49]White solid(129 mg, 59%); Time: 12h; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.87 (br s, 1H), 8.12 (s, 1H), 8.02 (s, 1H), 4.30 (br s, 2H), 3.80 (br s, 2H), 1.73 (br s, 4H), 1.44 (br s, 4H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 154.0 (s, 1C), 152.3 (s, 1C), 151.5 (s, 1C), 138.3 (s, 1C), 118.9 (s, 1C), 49.4 (s, 1C), 48.0 (s, 1C), 29.1 (s, 1C), 27.1 (s, 1C), 26.7 (s, 2C). Anal.Calcd (%) for $C_{11}H_{15}N_5$: C, 60.81; H, 6.96; N, 32.23. Found: C, 60.95; H, 6.80; N, 32.31.

(2R,3R,4S,5R)-2-(6-(Azetidin-1-yl)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (5y). Off white solid(185 mg, 60%); mp 208-210°C; Time: 12h;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (s, 1H), 8.16 (s, 1H), 5.85 (d, *J* = 5.8 Hz, 1H), 5.39 (d, *J* = 5.8 Hz, 1H), 5.33 (dd, *J* = 6.0, 4.5 Hz, 1H), 5.13 (d, *J* = 3.9 Hz, 1H), 4.55 (dd, *J* = 10.9, 5.3 Hz, 1H), 4.32 (br s, 4H), 4.11 (d, *J* = 2.9 Hz, 1H), 3.92 (d, *J* = 2.6 Hz, 1H), 3.66–3.61 (m, 1H), 3.54–3.48 (m, 1H), 2.44–2.36 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 154.9 (s, 1C), 152.5 (s, 1C), 149.7 (s, 1C), 140.5 (s, 1C), 120.2 (s, 1C), 88.3 (s, 1C), 86.3 (s, 1C), 73.9 (s, 1C), 71.0 (s, 1C), 62.0 (s, 1C), 51.9 (s, 2C), 17.6 (s, 1C). Anal.Calcd (%) for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.91; H, 5.44; N, 22.91.HRMS (ESI-TOF): *m*/*z* [M + H]$^+$calcd for $C_{13}H_{18}N_5O_4$: 308.1359; found: 308.1365.

(2R,3S,4R,5R)-2-(Hydroxymethyl)-5-(6-morpholino-9H-purin-9-yl)tetrahydrofuran-3,4-diol (5z).[46] White solid(311 mg, 92%); Time: 12h;^{1}H NMR (400 MHz, DMSO-d_6) δ8.39 (s, 1H), 8.23 (s, 1H), 5.89 (d, *J* = 5.8 Hz, 1H), 5.42 (d, *J* = 6.1 Hz, 1H), 5.27 (dd, *J* = 6.5, 4.7 Hz, 1H), 5.15 (d, *J* = 4.7 Hz, 1H), 4.54 (dd, *J* = 11.0, 5.6 Hz, 1H), 4.18 (br s, 4H), 4.12 (dd, *J* = 8.2, 4.6 Hz, 1H), 3.93 (d, *J* = 3.3 Hz, 1H), 3.68 (t, *J* = 4.6 Hz, 4H), 3.63 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.55–3.49 (m, 1H).^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 153.7 (s, 1C), 152.2 (s, 1C), 150.8 (s, 1C), 139.4 (s, 1C), 120.1 (s, 1C), 88.2 (s, 1C), 86.2 (s, 1C), 74.0 (s, 1C), 70.9 (s, 1C), 66.6 (s, 2C), 61.9 (s, 1C), 45.7 (s, 2C). Anal.Calcd (%) for $C_{14}H_{19}N_5O_5$: C, 49.85; H, 5.68; N, 20.76. Found: C, 49.93; H, 5.52; N, 20.84.

(2R,3S,4R,5R)-2-(Hydroxymethyl)-5-(6-(piperidin-1-yl)-9H-purin-9-yl)tetrahydrofuran-3,4-diol (5aa).[46] White solid(302 mg, 90%); Time: 12h;^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s,

1H), 8.18 (s, 1H), 5.88 (d, *J* = 5.9 Hz, 1H), 5.41 (d, *J* = 6.1 Hz, 1H), 5.33 (dd, *J* = 6.4, 4.6 Hz, 1H), 5.14 (d, *J* = 4.7 Hz, 1H), 4.55 (dd, *J* = 11.0, 5.8 Hz, 1H), 4.44–3.98 (m, 5H), 3.93 (d, *J* = 3.1 Hz, 1H), 3.69–3.60 (m, 1H), 3.57–3.48 (m, 1H), 1.73–1.60 (m, 2H), 1.59–1.44 (m, 4H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 153.6 (s, 1C), 152.2 (s, 1C), 150.6 (s, 1C), 138.9 (s, 1C), 119.9 (s, 1C),88.2 (s, 1C), 86.2 (s, 1C), 73.9 (s, 1C), 71.0 (s, 1C), 62.0 (s, 1C), 46.1 (s, 2C), 26.1 (s, 2C), 24.7 (s, 1C). Anal.Calcd (%) for $C_{15}H_{21}N_5O_4$: C, 53.72; H, 6.31; N, 20.88.Found: C, 53.80; H, 6.15; N, 20.76.

(2R,3R,4S,5R)-2-(6-(Azepan-1-yl)-9H-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (5ab).[50]White solid(224 mg, 64%); Time: 12h;^{1}H NMR (400 MHz, DMSO-d_6) δ8.32 (s, 1H), 8.17 (s, 1H), 5.87 (d, *J* = 6.0 Hz, 1H), 5.40 (d, *J* = 6.2 Hz, 1H), 5.34 (dd, *J* = 6.8, 4.6 Hz, 1H), 5.13 (d, *J* = 4.6 Hz, 1H), 4.57 (dd, *J* = 11.1, 5.9 Hz, 1H), 4.29 (br s, 2H), 4.11 (dd, *J* = 7.8, 4.6 Hz, 1H), 3.93 (d, *J* = 3.1 Hz, 1H), 3.82 (br s, 2H), 3.66–3.61 (m, 1H), 3.55–3.49 (m, 1H), 1.74 (br s, 4H), 1.45 (br s, 4H). $^{13}C\{^{1}H\}$ NMR(101 MHz, DMSO-d_6) δ 154.1 (s, 1C), 152.3 (s, 1C), 150.4 (s, 1C), 139.2 (s, 1C), 119.8 (s, 1C), 88.2 (s, 1C), 86.2 (s, 1C), 73.8 (s, 1C), 71.0 (s, 1C), 62.0 (s, 1C), 49.5 (s, 1C), 48.2 (s, 1C), 29.0 (s, 1C), 27.0 (s, 1C), 26.6 (s, 2C). Anal.Calcd (%) for $C_{16}H_{23}N_5O_4$: C, 55.00; H, 6.64; N, 20.04. Found: C, 55.12; H, 6.50; N, 20.14.

2-Chloro-6-(piperidin-1-yl)-9H-purine (7a).[46]White solid(167 mg, 70%);Time: 12h;^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (br s, 1H), 8.07 (s, 1H), 4.11 (br s, 4H), 1.69–1.59 (m, 2H), 1.59–1.47 (m, 4H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 153.6 (s, 1C), 153.0 (s, 1C), 152.9 (s, 1C), 138.7 (s, 1C), 118.0 (s, 1C),46.3 (s, 2C), 26.1 (s, 2C), 24.5 (s, 1C).Anal.Calcd(%) for $C_{10}H_{12}ClN_5$: C, 50.53; H, 5.09; N, 29.46. Found: C, 50.67; H, 5.01; N, 29.58.

2-Chloro-6-((4-methoxyphenyl)thio)-9H-purine (7b).[35]White solid(229 mg, 78%); Time: 12h;^{1}H NMR (400 MHz, DMSO-d_6) δ13.68 (br s, 1H), 8.49 (s, 1H), 7.52 (d, J = 8.2 Hz, 2H), 7.04 (d, J = 8.2 Hz, 2H), 3.80 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.1 (s, 1C), 159.5 (s, 1C), 152.5 (s, 1C), 152.5 (s, 1C), 145.3 (s, 1C), 137.6 (s, 2C), 129.6 (s, 1C), 116.6 (s, 1C), 115.5 (s, 2C), 55.8 (s, 1C). Anal.Calcd (%) for $C_{12}H_9ClN_4OS$: C, 49.24; H, 3.10; N, 19.14; S, 10.95.Found: C, 49.42; H, 3.04; N, 19.22; S, 10.89.

2-Chloro-4-(piperidin-1-yl)pyrimidine (7c).[51]White solid(168 mg, 85%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 6.1 Hz, 1H), 6.35 (d, J = 6.1 Hz, 1H), 3.59 (br s, 4H), 1.72–1.64 (m, 2H), 1.64–1.53 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.3 (s, 1C), 160.8 (s, 1C), 156.9 (s, 1C), 101.0 (s, 1C), 45.2 (s, 2C), 25.4 (s, 2C), 24.3 (s, 1C). Anal.Calcd (%) for $C_9H_{12}ClN_3$: C, 54.69; H, 6.12; N, 21.26. Found: C, 54.80; H, 6.04; N, 21.38.

2-Chloro-4-(phenylthio)pyrimidine (7d).[52]White solid(196 mg, 88%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 5.4 Hz, 1H), 7.64–7.55 (m, 2H), 7.54–7.45 (m, 3H), 6.60 (d, J = 5.4 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 176.6 (s, 1C), 160.6 (s, 1C), 157.6 (s, 1C), 135.7 (s, 2C),130.6 (s, 1C), 130.2 (s, 2C),127.0 (s, 1C), 115.2 (s, 1C).Anal.Calcd (%) for $C_{10}H_7ClN_2S$: C, 53.94; H, 3.17; N, 12.58; S, 14.40. Found: C, 53.82; H, 3.07; N, 12.72; S, 14.46.

4-(2-Chloropyrimidin-4-yl)morpholine (7e).[12e]White solid(176 mg, 88%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 5.7 Hz, 1H), 6.37 (d, J = 5.8 Hz, 1H), 3.80–3.70 (m, 4H), 3.62 (br s, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.8 (s, 1C), 160.8 (s, 1C), 157.4 (s, 1C), 101.1 (s, 1C), 66.3 (s, 2C), 44.2 (s, 2C).Anal.Calcd (%) for $C_8H_{10}ClN_3O$: C, 48.13; H, 5.05; N, 21.05. Found: C, 48.21; H, 5.01; N, 21.17.

2,4-Dichloro-6-(phenylthio)pyrimidine (7f).[53]White solid(201 mg, 78%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.50 (m, 5H), 6.57 (s, 1H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 177.7 (s, 1C), 161.5 (s, 1C), 159.8 (s, 1C), 135.6 (s, 2C), 131.0 (s, 1C), 130.4 (s, 2C), 126.2 (s, 1C), 114.6 (s, 1C). Anal.Calcd (%) for $C_{10}H_6Cl_2N_2S$: C, 46.71; H, 2.35; N, 10.89; S, 12.47.Found: C, 46.83; H, 2.21; N, 10.77; S, 12.55.

2,4-Di(piperidin-1-yl)pyrimidine (8a).Yellow solid(210 mg, 85%);mp 52-54 ^{o}C; Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 5.3 Hz, 1H), 5.79 (d, J = 5.4 Hz, 1H), 3.70 (br s, 4H), 3.52 (br s, 4H), 1.74–1.42 (m, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.2 (s, 1C), 161.6 (s, 1C), 156.3 (s, 1C), 92.2 (s, 1C), 44.8 (s, 2C), 44.8 (s, 2C), 25.8 (s, 2C), 25.5 (s, 2C), 25.0 (s, 1C), 24.8 (s, 1C). Anal.Calcd (%) for $C_{14}H_{22}N_4$: C, 68.26; H, 9.00; N, 22.74. Found: C, 68.40; H, 8.96; N, 22.62.HRMS (ESI-TOF): m/z $[M + H]^+$calcd for $C_{14}H_{23}N_4$: 247.1923; found: 247.1931.

4,4'-(Pyrimidine-2,4-diyl)dimorpholine (8b).[12e]Yellow solid(236 mg, 94%);Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 6.0 Hz, 1H), 5.85 (d, J = 6.0 Hz, 1H), 3.77–3.66 (m, 12H), 3.54 (t, J = 4.7 Hz, 4H).^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.6 (s, 1C), 161.4 (s, 1C), 156.6 (s, 1C), 93.1 (s, 1C), 66.9 (s, 2C), 66.5 (s, 2C), 44.3 (s, 2C), 44.1 (s, 2C).Anal.Calcd (%) for $C_{12}H_{18}N_4O_2$: C, 57.58; H, 7.25; N, 22.38. Found: C, 57.70; H, 7.09; N, 22.46.

4-(4-(Phenylthio)pyrimidin-2-yl)morpholine (9a).Colorless oil(230 mg, 84%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ7.95 (d, J = 5.3 Hz, 1H), 7.62–7.52 (m, 2H), 7.47–7.37 (m, 3H), 6.04 (d, J = 5.3 Hz, 1H), 3.69 (br s, 8H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.3 (s, 1C), 160.7 (s, 1C), 156.5 (s, 1C), 135.8 (s, 2C), 129.6 (s, 1C), 129.4 (s, 2C), 128.6 (s, 1C), 106.2 (s, 1C), 66.7

(s, 2C), 44.1 (s, 2C).Anal.Calcd (%) for $C_{14}H_{15}N_3OS$: C, 61.52; H, 5.53; N, 15.37; S, 11.73. Found: C, 61.66; H, 5.45; N, 15.49; S, 11.80.HRMS (ESI-TOF): *m*/*z* $[M + H]^+$calcd for $C_{14}H_{16}N_3OS$: 274.1014; found: 274.1018.

4-(Phenylthio)-2-(piperidin-1-yl)pyrimidine (9b).Colorless oil(237 mg, 87%); Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 5.2 Hz, 1H), 7.57 (dd, *J* = 6.3, 3.0 Hz, 2H), 7.44–7.38 (m, 3H), 5.94 (d, *J* = 5.2 Hz, 1H), 3.66 (t, *J* = 5.3 Hz, 4H), 1.64–1.59 (m, 2H), 1.54–1.50 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ172.0 (s, 1C), 160.6 (s, 1C), 156.5 (s, 1C), 135.8 (s, 2C), 129.4 (s, 1C), 129.3 (s, 2C), 129.0 (s, 1C), 105.0 (s, 1C), 44.7 (s, 2C), 25.7 (s, 2C), 24.8 (s, 1C).Anal.Calcd (%) for $C_{15}H_{17}N_3S$: C, 66.39; H, 6.31; N, 15.48; S, 11.81. Found: C, 66.51; H, 6.15; N, 15.38; S, 11.69.HRMS (ESI-TOF): *m*/*z* $[M + H]^+$calcd for $C_{15}H_{18}N_3S$: 272.1221; found: 272.1227.

5-Chloro-2-(((4-(1-(2-chloro-9H-purin-6-yl)piperidin-4-yl)-2-isopropoxy-5-methylphenyl)amino)methyl)-N-(2-(isopropylsulfonyl)phenyl)pyrimidin-4-amine (11a).White solid(457 mg, 63%); mp 262-264 ^oC; Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 13.18 (br s, 1H), 9.50 (s, 1H), 8.57 (d, *J* = 8.3 Hz, 1H), 8.15 (d, *J* = 2.3 Hz, 1H), 8.03 (d, *J* = 1.6 Hz, 1H), 7.93 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 2.2 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.53 (s, 1H), 7.30–7.21 (m, 2H), 6.70 (s, 1H), 5.73 (br s, 2H), 4.53–4.46 (m, 1H), 3.39–2.93 (m, 5H), 2.22 (s, 3H), 1.97 (d, *J* = 11.2 Hz, 2H), 1.81–1.70 (m, 2H), 1.38–1.23 (m, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.4 (s, 1C), 155.3 (s, 1C), 153.8 (s, 1C), 153.0 (s, 1C), 152.5 (s, 1C), 144.7 (s, 1C), 141.3 (s, 1C), 138.5 (s, 1C), 136.7 (s, 1C), 136.6 (s, 1C), 134.6 (s, 1C), 131.2 (s, 1C), 127.9 (s, 1C), 126.9 (s, 1C), 124.9 (s, 1C), 123.6 (s, 1C), 123.1 (s, 1C), 120.7 (s, 1C), 118.4 (s, 1C), 110.9 (s, 1C),

105.8 (s, 1C),71.6 (s, 1C), 55.5 (s, 1C), 54.2(s, 1C),46.2 (s, 2C), 38.4 (s, 1C), 32.9 (s, 2C),22.2 (s, 2C), 19.0 (s, 1C),15.3 (s, 2C).Anal.Calcd (%) for $C_{34}H_{39}Cl_2N_9O_3S$: C, 56.35; H, 5.42; N, 17.40; S, 4.42.Found: C, 56.53; H, 5.28; N, 17.26; S, 4.46. HRMS (ESI-TOF): *m*/*z* [M + H]$^+$calcd for $C_{34}H_{40}Cl_2N_9O_3S$: 724.2352; found: 724.2360.

2-(((4-(1-(9H-Purin-6-yl)piperidin-4-yl)-2-isopropoxy-5-methylphenyl)amino)methyl)-5-chloro-N-(2-(isopropylsulfonyl)phenyl)pyrimidin-4-amine (11b). White solid(477 mg, 69%); mp 232-234 ^{o}C; Time: 12h;^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.57 (dd, *J* = 8.1, 2.3 Hz, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 8.14 (d, *J* = 3.4 Hz, 1H), 8.02 (d, *J* = 2.5 Hz, 1H), 7.96 (d, *J* = 3.2 Hz, 1H), 7.94–7.89 (m, 1H), 7.62 (t, *J* = 7.0 Hz, 1H), 7.53 (d, *J* = 2.3 Hz, 1H), 7.31–7.16 (m, 2H), 6.71 (d, *J* = 2.5 Hz, 1H), 5.74 (br s, 2H), 4.52–4.45 (m, 1H), 3.34–2.95 (m, 5H), 2.22 (s, 3H), 1.96 (d, *J* = 12.3 Hz, 2H), 1.80–1.71 (m, 2H), 1.37–1.22 (m, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.4 (s, 1C), 155.3 (s, 1C), 153.9 (s, 1C), 151.7 (s, 1C), 151.2 (s, 1C), 144.7 (s, 1C), 140.4 (s, 1C), 138.5 (s, 1C), 137.0 (s, 1C), 136.5 (s, 1C), 134.6 (s, 1C), 131.2 (s, 1C), 127.8 (s, 1C), 126.9 (s, 1C), 124.9 (s, 1C), 123.7 (s, 1C), 123.1 (s, 1C), 120.7 (s, 1C), 119.5 (s, 1C), 110.9 (s, 1C), 105.8 (s, 1C), 71.6 (s, 1C), 55.4 (s, 1C), 54.4 (s, 1C), 46.2 (s, 2C), 38.6 (s, 1C), 33.0 (s, 2C), 22.2 (s, 2C), 19.0 (s, 1C), 15.3 (s, 2C). Anal.Calcd (%) for $C_{34}H_{40}ClN_9O_3S$: C, 59.16; H, 5.84; N, 18.26; S, 4.64.Found: C, 59.32; H, 5.66; N, 18.40; S, 4.56.HRMS (ESI-TOF): *m*/*z* [M + H]$^+$calcd for $C_{34}H_{41}ClN_9O_3S$: 690.2742; found: 690.2748.

Methyl 7-(4-(benzo[d]oxazol-2-yl)piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate (11c). White solid(226 mg, 50%); mp228-230^{o}C;Time: 12h;^{1}H NMR (500MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.14 (d, *J* = 13.0 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 7.9 Hz,

1H), 7.19 (td, J = 7.7, 1.0 Hz, 1H), 7.06 (td, J = 7.9, 1.1 Hz, 1H), 6.79 (d, J = 6.7 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.96–3.90 (m, 7H), 3.36 (t, J = 5.0 Hz, 4H), 1.54 (t, J = 7.2 Hz, 3H).$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ172.9 (s, 1C), 166.5 (s, 1C), 161.9 (s, 1C), 153.2 (d, $J_{C,F}$ = 249.5 Hz, 1C), 148.8 (s, 1C), 148.3 (s, 1C), 144.4 (d, $J_{C,F}$ = 10.8 Hz, 1C), 142.8 (s, 1C), 136.1 (d, $J_{C,F}$ = 1.6 Hz, 1C),124.6 (d, $J_{C,F}$ = 6.9 Hz, 1C), 124.2 (s, 1C), 121.1 (s, 1C), 116.5 (s, 1C), 114.1 (d, $J_{C,F}$ = 23.0Hz, 1C), 110.4 (s, 1C), 108.9 (s, 1C), 104.3 (d, $J_{C,F}$ = 2.7 Hz, 1C), 52.1 (s, 1C), 49.6 (s, 1C), 49.5 (s, 1C), 48.9 (s, 1C), 45.6 (s, 2C), 14.4 (s, 1C).Anal.Calcd (%) for $C_{24}H_{23}FN_4O_4$: C, 63.99; H, 5.15; N, 12.44. Found: C, 63.87; H, 5.23; N, 12.52.HRMS (ESI-TOF): m/z $[M + H]^+$calcd for $C_{24}H_{24}FN_4O_4$: 451.1782; found: 451.1790.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

^1H and ^{13}C NMR spectra of all compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: ar.kapdi@ictmumbai.edu.in

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a)Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs.*J. Med. Chem.***2014**, *57*, 5845-5859. (b) Gomtsyan, A. Heterocycles in drugs and drug discovery. *Chem. Heterocycl. Compd.***2012**, *48*, 7-10.

(2) (a) Lamberth, C. Heterocyclic chemistry in crop protection.*Pest.Manag. Sci.***2013**, *69*, 1106-1114. (b) Lamberth, C.; Dinges, J. In Bioactive Heterocyclic Compounds: Agrochemicals. Eds. Lamberth, C.; Dinges, J. Wiley-VCH, Verlag, **2012**.

(3) (a) Ghosh, T.; Lehmann, M.Recent advances in heterocycle-based metal-free calamitics.*J. Mater. Chem. C***2017**, *5*, 12308-12337. (b) Chen, D.; Su, S.-J.; Cao, Y. Nitrogen heterocycle-containing materials for highly efficient phosphorescent OLEDs with low operating voltage.*J. Mater. Chem. C***2014**, *2*, 9565-9578. (c) Mercs, L.; Albrecht, M. Beyond catalysis: *N*-heterocyclic carbene complexes as components for medicinal, luminescent, and functional materials applications.*Chem. Soc. Rev.***2010**, *39*, 1903-1912.

(4) (a) Feng, M.; Tang, B.; Liang, S. H.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry.*Curr.Top. Med. Chem.***2016**, *16*, 1200-1216.

(b) Landelle, G.; Panossian, A.; Leroux, F. R. Trifluoromethyl Ethers and –Thioethers as Tools for Medicinal Chemistry and Drug Discovery.*Curr.Top. Med. Chem.***2014**, *14*, 941-951.

(5) Vyhnalkova, R.; Eisenberg, A.; van de Ven, T. G. M. Deactivation Efficiency of Stabilized Bactericidal Emulsions.*Langmuir***2011**, *27*, 11296-11305.

(6) Whisnant, J. K.; Pelkey, J. Rheumatoid arthritis: treatment with azathioprine (IMURAN (R)). Clinical side-effects and laboratory abnormalities.*Ann. Rheum. Dis.***1982**, *41*, 44-47.

(7) (a) Sirohi, B.; Rastogi, S.; Dawood, S. Buparlisib in breast cancer.*Future Oncol.***2015**,*11*, 1463-1470. (b) Speranza, M.-C.; Nowicki, M. O.; Behera, P.; Cho, C.-F.; Chiocca, E. A.; Lawler, S. E. BKM-120 (Buparlisib): A Phosphatidyl-Inositol-3 Kinase Inhibitor with Anti-Invasive Properties in Glioblastoma.*Sci. Rep*. **2016**, *6*, 20189.

(8) (a) Kong, D.-x.;Yamori, T. ZSTK474, a novel phosphatidylinositol 3-kinase inhibitor identified using the JFCR39 drug discovery system.*ActaPharmacol.Sin.***2010**, *31*, 1189-1197. (b) Cope, C. L.; Gilley, R.; Balmanno, K.; Sale, M. J.; Howarth, K. D.; Hampson, M.; Smith, P. D.; Guichard, S. M.; Cook, S. J. Adaptation to mTOR kinase inhibitors by amplification of eIF4E to maintain cap-dependent translation.*J. Cell Sci*. **2014**, *127*, 788-800.

(9) Sitbon, O.; Morrell, N. Pathways in pulmonary arterial hypertension: the future is here.*Eur. Respir. Rev*. **2012**, *21*, 321-327.

(10) Thioetherification of heterocycles *via*uncatalysed processes: (a) Campbell, J. R. Synthesis of Thioethers. Amide Solvent-Promoted Nucleophilic Displacement of Halide by Thiolate Ion.*J. Org. Chem.***1964**, *29*, 1830-1833. (b) Adams, R.; Ferretti, A. Thioethers. III. Preparation of Aromatic Di- and Tri-mercapto Compounds by Dealkylation of Aryl Alkyl Thioethers.*J. Am. Chem. Soc.***1959**, *81*, 4939-4940.

(11) Metal-mediated thioetherification: (a) Itoh, T.; Mase, T. A General Palladium-Catalyzed Coupling of Aryl Bromides/Triflates and Thiols.*Org. Lett.* **2004**, *6*, 4587–4590. (b) Jones, K. D.; Power, D. J.; Bierer, D.; Gericke, K. M.; Stewart, S. G. Nickel Phosphite/Phosphine-Catalyzed C–S Cross-Coupling of Aryl Chlorides and Thiols.*Org. Lett.* **2018**, *20*, 208–211. (c) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. A General and Long-Lived Catalyst for the Palladium-Catalyzed Coupling of Aryl Halides with Thiols.*J. Am. Chem. Soc.* **2006**, *128*, 2180–2181. (d) Platon, M.; Wijaya, N.; Rampazzi, V.; Cui, L.; Rousselin, Y.; Saeys, M.; Hierso, J.-C. Thioetherification of Chloroheteroarenes: A Binuclear Catalyst Promotes Wide Scope and High Functional-Group Tolerance.*Chem.-Eur. J.* **2014**, *20*, 12584–12594.

(12) Metal-mediated amination: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. L. Rational Development of Practical Catalysts for Aromatic Carbon−Nitrogen Bond Formation.*Acc. Chem. Res.* **1998**, *31*, 805-818. (b) Hartwig, J. F. Evolution of a Fourth Generation Catalyst for the Amination and Thioetherification of Aryl Halides.*Acc. Chem. Res*. **2008**, *41*, 1534-1544. (c) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. Rapid Room Temperature Buchwald–Hartwig and Suzuki–Miyaura Couplings of Heteroaromatic Compounds Employing Low Catalyst Loadings.*Chem.-Eur. J.* **2006**, *12*, 5142-5148. (d) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C–N Cross-Coupling Reactions.*Chem. Rev.* **2016**, *116*, 12564-12649. (e) Murthy Bandaru, S.; Bhilare, S.; Chrysochos, N.; Gayakhe, V.; Trentin, I.; Schulzke, C.; Sanghvi, Y. S.; Kapdi, A. R. Pd/PTABS: Catalyst for Room Temperature Amination of Heteroarenes.*Org. Lett.***2018**, *20*, 473-476.

(13) Amination of heterocycles *via*S_NAr: (a) Vorbruggen, H. Advances in amination of nitrogen heterocycles. *Adv. Heterocycl. Chem*. **1990**, *49*, 117-192. (b) Walsh, K.;

Sneddon, H. F.; Moody, C. J. Amination of Heteroaryl Chlorides: Palladium Catalysis or S_NAr in Green Solvents?. *ChemSusChem*.**2013**, *6*, 1455-1460.(c) Metal and base-free S_NAr: Sreedhar, B.; Reddy, P.; Reddy, M. Catalyst-Free and Base-Free Water-Promoted S_NAr Reaction of Heteroaryl Halides with Thiols. *Synthesis***2009**, 1732–1738.

(14) (a) Dyson, P. J.; Jessop, P. G. Solvent effects in catalysis: rational improvements of catalysts *via* manipulation of solvent interactions.*Catal. Sci. Technol.***2016**, *6*, 3302-3316. (b) Varghese, J. J.; Mushrif, S. H. Origins of complex solvent effects on chemical reactivity and computational tools to investigate them: a review.*React. Chem. Eng.***2019**, *4*, 165-206.

(15) (a) Colomer, I.; Chamberlain, A. E. R.; Haughney, M. B.; Donohoe, T. J. Hexafluoroisopropanol as a highly versatile solvent.*Nat. Rev. Chem.***2017**, *1*, 0088. (b) Bentley, T. W.; Llewellyn, G.; Ryu, Z. H. Solvolytic Reactions in Fluorinated Alcohols. Role of Nucleophilic and Other Solvation Effects.*J. Org. Chem.* **1998**, *63*, 4654-4659.

(16) (a) Wencel-Delord, J.; Colobert, F. A remarkable solvent effect of fluorinated alcohols on transition metal catalysed C–H functionalizations.*Org. Chem. Front.***2016**, *3*, 394-400.(b) Conway, Jr., J. H.; Rovis, T. RegiodivergentIridium(III)-Catalyzed Diamination of Alkenyl Amides with Secondary Amines: Complementary Access to γ- or δ-Lactams. *J. Am. Chem. Soc.***2018**, *140*, 135-138. (c) Zhu, Y.; Colomer, I.; Thompson, A. L.; Donohoe, T. J. HFIP Solvents Enables Alcohols To Act as Alkylating Agents in StereoselectiveHeterocyclization. *J. Am. Chem. Soc*. **2019**, *141*, 6489-6493.

(17) (a) Perez, J. M.; Maquilon, C.; Ramon, D. J.; Baeza, A. Hexafluoroisopropanol-Promoted Metal-Free Allylation of Silyl Enol Ethers with Allylic Alcohols. *Asian J. Org. Chem.***2017**, *6*, 1440-1444. (b) Zhou, Z.; Cheng, Q.-Q.; Kürti, L. Aza-

RubottomOxidation: Synthetic Access to Primary α-Aminoketones. *J. Am. Chem. Soc*. **2019**, *141*, 2242-2246. (c) Colomer, I.; Barcelos, R. C.; Christensen, K. E.; Donohoe, T. J. Orthogonally Protected 1,2-Diols from Electron-Rich Alkenes Using Metal-Free Olefin *syn*-Dihydoxylation. *Org. Lett.***2016**, *18*, 5880-5883.

(18) Vekariya, R. H.; Aubé, J. Hexafluoro-2-propanol-Promoted Intermolecular Friedel–Crafts Acylation Reaction.*Org. Lett.***2016**, *18*, 3534-3537.

(19) Cativiela, C.; Garcia, J. I.; Mayoral, J. A.; Salvatella, L. On the role of hexafluoroisopropanol in Diels–Alder reactions of acid-sensitive reagents.*Can J. Chem.***1994**, *72*, 308-311.

(20) Sinha, S. K.; Bhattacharya, T.; Maiti, D. Role of hexafluoroisopropanol in C–H activation.*React. Chem. Eng.***2019**, *4*, 244-253.

(21) De, K.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. Solvent-Promoted and -Controlled Aza-Michael Reaction with Aromatic Amines.*J. Org. Chem.***2009**, *74*, 6260-6265.

(22) Saya, J. M.; Berabez, R.; Broersen, P.; Schuringa, I.; Kruithof, A.; Orru, R. V. A.; Ruijter, E. Hexafluoroisopropanol as the Acid Component in the Passerini Reaction: One-Pot Access to β-Amino Alcohols.*Org. Lett.* **2018**, *20*, 3988-3991.

(23) Tang, R.-J.; Milcent, T.; Crousse, B. Regioselective Halogenation of Arenes and Heterocycles in Hexafluoroisopropanol.*J. Org. Chem.***2018**, *83*, 930-938.

(24) Wang, M.; Qiao, Z.; Zhao, J.; Jiang, X. Palladium-Catalyzed Thiomethylation via a Three-Component Cross-Coupling Strategy.*Org. Lett.* **2018**,*20*, 6193–6197.

(25) Kapdi, A. R.; Taylor, R. J. K.; Fairlamb, I. J. S. Highly regio- and chemoselective palladium(0)-mediated allylic substitution of difunctional allylic halides with phenols.*Tetrahedron Lett.***2010**, *51*, 6378-6380.

(26) Kapdi, A. R.; Prajapati, D. Regioselective palladium-catalysed cross-coupling reactions: a powerful synthetic tool.*RSC Adv.* **2014**, *4*, 41245-41259.

(27) Nix, N. M.; Brown, K. S. Ceritinib for *ALK*-Rearrangement-Positive Non-Small Cell Lung Cancer.*J. Adv. Pract. Oncol.***2015**, *6*, 156-160.

(28) Ratnikov, M. O.; Tumanov, V. V.; Smit, W. A. Elaboration of a Lewis acid-free protocol for the alkylation of silicon-containing π-donors by β-arylthioalkyl chlorides. *Tetrahedron***2010**, *66*, 1832-1836.

(29) Ishitobi, K.; Isshiki, R.; Asahara, K. K.; Lim, C.; Muto, K.; Yamaguchi, J.Decarbonylative Aryl Thioether Synthesis by Ni Catalysis.*Chem. Lett.***2018**, *47*, 756–759.

(30) Bandaru, S. S. M.; Bhilare, S.; Cardozo, J.; Chrysochos, N.; Schulzke, C.; Sanghvi, Y. S.; Gunturu, K. C.; Kapdi, A. R. Pd/PTABS: Low-Temperature Thioetherification of Chloro(hetero)arenes. *J. Org. Chem.***2019**, *84*, 8921–8940.

(31) Kibriya, G.; Mondal, S.; Hajra, A.Visible-Light-Mediated Synthesis of Unsymmetrical Diaryl Sulfides via Oxidative Coupling of Arylhydrazine with Thiol.*Org. Lett.***2018**, *20*, 7740–7743.

(32) Arisawa, M.; Toriyama, F.; Yamaguchi, M.Rhodium-catalyzed phenylthiolation reaction of heteroaromatic compounds using α-(phenylthio)isobutyrophenone.*Tetrahedron Lett.***2011**, *52*, 2344–2347.

(33) Gandeepan, P.; Mo, J.; Ackermann, L.Photo-induced copper-catalyzed C–H chalcogenation of azoles at room temperature.*Chem. Commun.***2017**, *53*, 5906–5909.

(34) Laufer, S. A.; Domeyer, D. M.; Scior, T. R. F.; Albrecht, W.; Hauser, D. R. J.Synthesis and Biological Testing of Purine Derivatives as Potential ATP-Competitive Kinase Inhibitors.*J. Med. Chem.*__2005__, *48*, 710–722.

(35) Pathak, A. K.; Pathak, V.; Seitz, L. E.; Suling, W. J.; Reynolds, R. C.Antimycobacterial Agents. 1. Thio Analogues of Purine.*J. Med. Chem.*__2004__, *47*, 273–276.

(36) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. A Metal-Free Amination of Benzoxazoles – The First Example of an Iodide-Catalyzed Oxidative Amination of Heteroarenes. *Org. Lett.*__2011__, *13*, 3754–3757.

(37) Cioffi, C. L.; Lansing, J. J.; Yüksel, H. Synthesis of 2-Aminobenzoxazoles Using Tetramethyl Orthocarbonate or 1,1-Dichlorodiphenoxymethane. *J. Org. Chem.*__2010__, *75*, 7942–7945.

(38) Wang, X.; Xu, D.; Miao, C.; Zhang, Q.; Sun, W. *N*-Bromosuccinimide as an oxidant for the transition-metal-free synthesis of 2-aminobenzoxazoles from benzoxazoles and secondary amines. *Org. Biomol. Chem.*__2014__, *12*, 3108–3113.

(39) Monge, A.; Pena, M. del C.; Palop, J. A.; Caldero, J. M.; Roca, J.; Garcia, E.; Romero, G.; del Rio, J.; Lasheras, B. Synthesis of 2-Piperazinylbenzothiazole and 2-Piperazinylbenzoxazole Derivatives with 5-HT_3 Antagonist and 5-HT_4 Agonist Properties. *J. Med. Chem.*__1994__, *37*, 1320–1325.

(40) Verma, S. K.; Acharya, B. N.; Kaushik, M. P. Chemospecific and ligand free CuI catalysed heterogeneous N-arylation of amines with diheteroaryl halides at room temperature. *Org. Biomol. Chem.*__2011__, *9*, 1324–1327.

(41) Dutta, P. K.; Sen, S.; Saha, D.; Dhar, B.Solid Supported Nano Structured Cu-Catalyst for Solvent/Ligand Free C_2 Amination of Azoles.*Eur. J. Org. Chem.*__2018__, *2018*, 657–665.

(42) Uday Kumar, R.; Reddy, K. H. V.; Anil Kumar, B. S. P.; Satish, G.; Reddy, V. P.; Nageswar, Y. V. D. Metal free amination of 2-chloroazoles in aqueous medium. *Tetrahedron Lett.***2016**, *57*, 637–640.

(43) Ho, L. A.; Raston, C. L.; Stubbs, K. A. Transition-Metal-Free Cross-Coupling Reactions in Dynamic Thin Films To Access Pyrimidine and Quinoxaline Analogues. *Eur. J. Org. Chem.***2016**, *2016*, 5957–5963.

(44) Regnier, G.; Canevari, R. J.; Laubie, M. J.; Le Douarec, J. C. Synthesis and vasodilator activity of new piperazine derivatives. *J. Med. Chem.***1968**, *11*, 1151–1155.

(45) Gulevskaya, A. V.; Maes, B. U. W.; Meyers, C.; Herrebout, W. A.; van der Veken, B. J. C–N Bond Formation by the Oxidative Alkylamination of Azines: Comparison of $AgPy_2MnO_4$ versus $KMnO_4$ as Oxidant. *Eur. J. Org. Chem.***2006**, *2006*, 5305–5314.

(46) Qu, G.-R.; Zhao, L.; Wang, D.-C.; Wu, J.; Guo, H.-M.Microwave-promoted efficient synthesis of C6-cyclo secondary amine substituted purine analogues in neat water.*Green Chem.***2008**, *10*, 287–289.

(47) Alves, M. J.; Carvalho, M. A.; Carvalho, S.; Dias, A. M.; Fernandes, F. H.; Proença, M. F.A New Approach to the Synthesis of*N,N*-Dialkyladenine Derivatives.*Eur. J. Org. Chem.***2007**, *2007*, 4881–4887.

(48) Huang, L.-K.; Cherng, Y.-C.; Cheng, Y.-R.; Jang, J.-P.; Chao, Y.-L.; Cherng,Y.-J. An efficient synthesis of substituted cytosines and purines under focused microwave irradiation.*Tetrahedron***2007**, *63*, 5323–5327.

(49)Huang, L.; Zhao, J.; Guo, J.; Huang, M.; You, Y.; Zheng, Y.*CN 109293727A*, 01 Feb**2019**.

(50) Vorbrüggen, H.; Krolikiewicz, K. Nucleosidsynthesen, XVIII. Aminierung von Heterocyclen, II. Einfache neue Synthese von N^6-substituierten Adenosinen und Adeninen sowie

ihrer 2-Amino- und 2-Hydroxyderivate. *Liebigs Ann. Chem.***1976**, *1976*, 745–761.

(51) Rasmussen, C. A. H.; Van Der Plas,H. C.; Grotenhuis, P.; Koudijs, A.Investigations into the *cine*-Amination of 4-Substituted-5-bromopyrimidines by potassium amide in liquid ammonia.*J. Heterocycl. Chem.***1978**, *15*, 1121–1125.

(52) Bourke, D. G.; Bu, X.; Burns, C. J.; Cuzzupe, A. N.; Feutrill, J. T.; Nero, T. L.; Blannin,B. M.; Zeng, J.; Gaynor,S. P. Thiopyrimidine-based compounds and uses thereof. *PCT Int. Appl.*2008092199, 07 Aug **2008**.

(53) Goudgaon, N. M.; Reddy, C. U.Efficient Synthesisof Novel 6-Phenylthio-2,4-disubstituted Pyrimidines.*Heterocycl. Commun.***2008**, *14*, 443–448.